Genetic Analysis of Brain Images from 21,000 People: The ENIGMA Project

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on behalf of the ENIGMA Consortium[2]

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Introduction: What is the ENIGMA Project?

- Worldwide Consortium – we **relate human brain images to genome-wide scans** (>500,000 common variants in your DNA)
- **Discover genetic variants that affect brain** / may also affect disease risk
- Enabled **largest brain imaging studies ever performed** (*Nature Genetics*, Apr 15 2012; 21,151 subjects, now increasing)
- 207 co-authors, 125 institutions, >500,000 SNPs, range of brain measures (massive global collaboration; "Crowd-sourcing")
- Founded 2009 by triumvirate of imaging genetics labs: Thompson (UCLA), Wright/Martin (Queensland), Franke (Netherlands), many more PIs & their teams run Working Groups
- Working Groups assess different brain measures – ENIGMA2 (morphometry), ENIGMA-DTI, ENIGMA-PIB, ENIGMA-Mouse, ENIGMA-PGC, Case-Control Working Groups ….

Why screen 21,000 brain images?

- **Amass a sample so vast that we can see how single-letter changes in your DNA affect the brain, in the midst of all the other factors that affect your brain (age, education, abused drugs, alcohol, body mass index, ..)**
- Do epidemiology with images (exercise, diet, medication)
- Discover genes that:

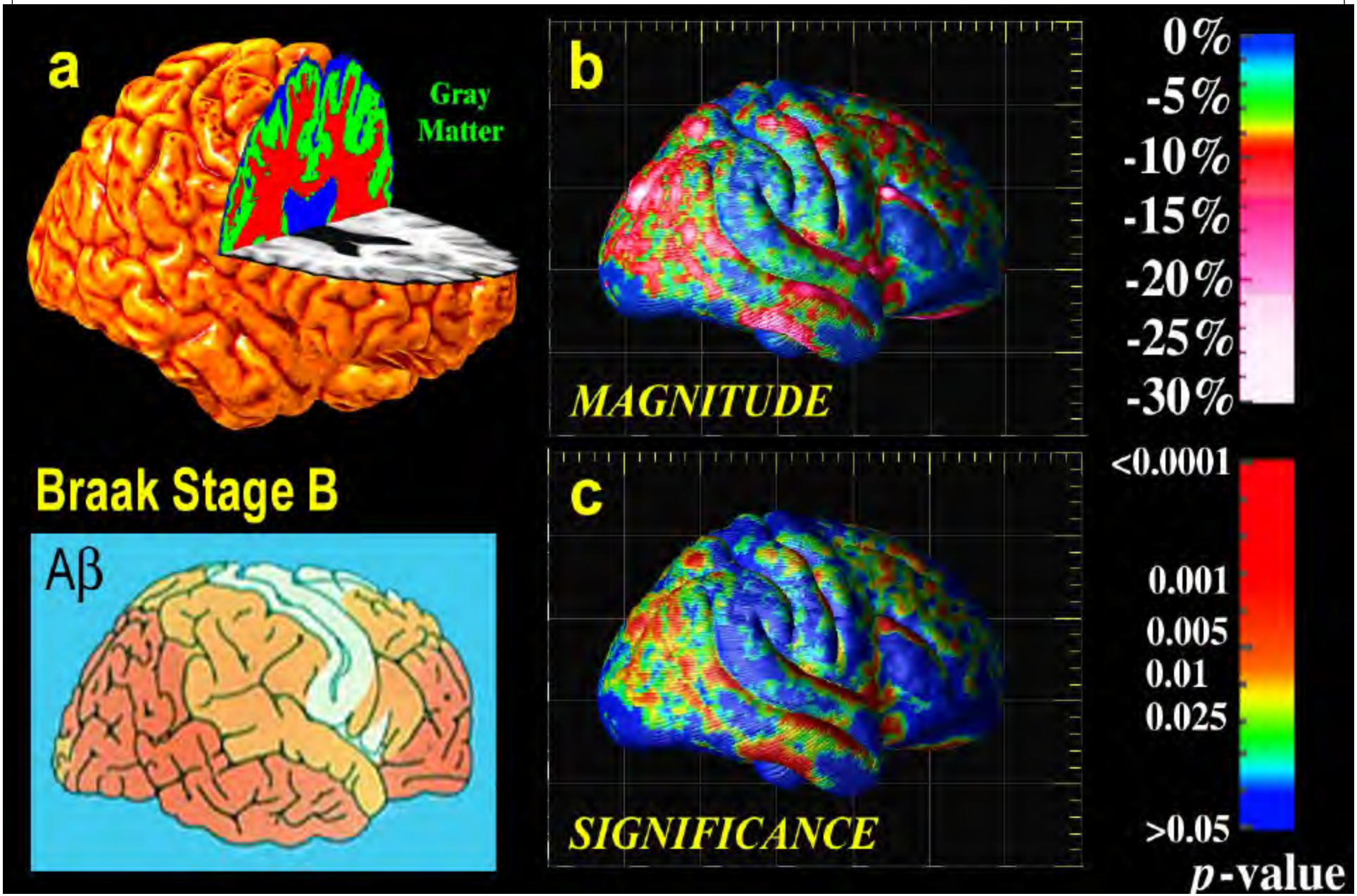
  - promote brain degeneration / risk for disease, affect brain wiring and organization (new leads in autism, Alzheimer's disease)

  - help estimate our **personal risk** of mental decline

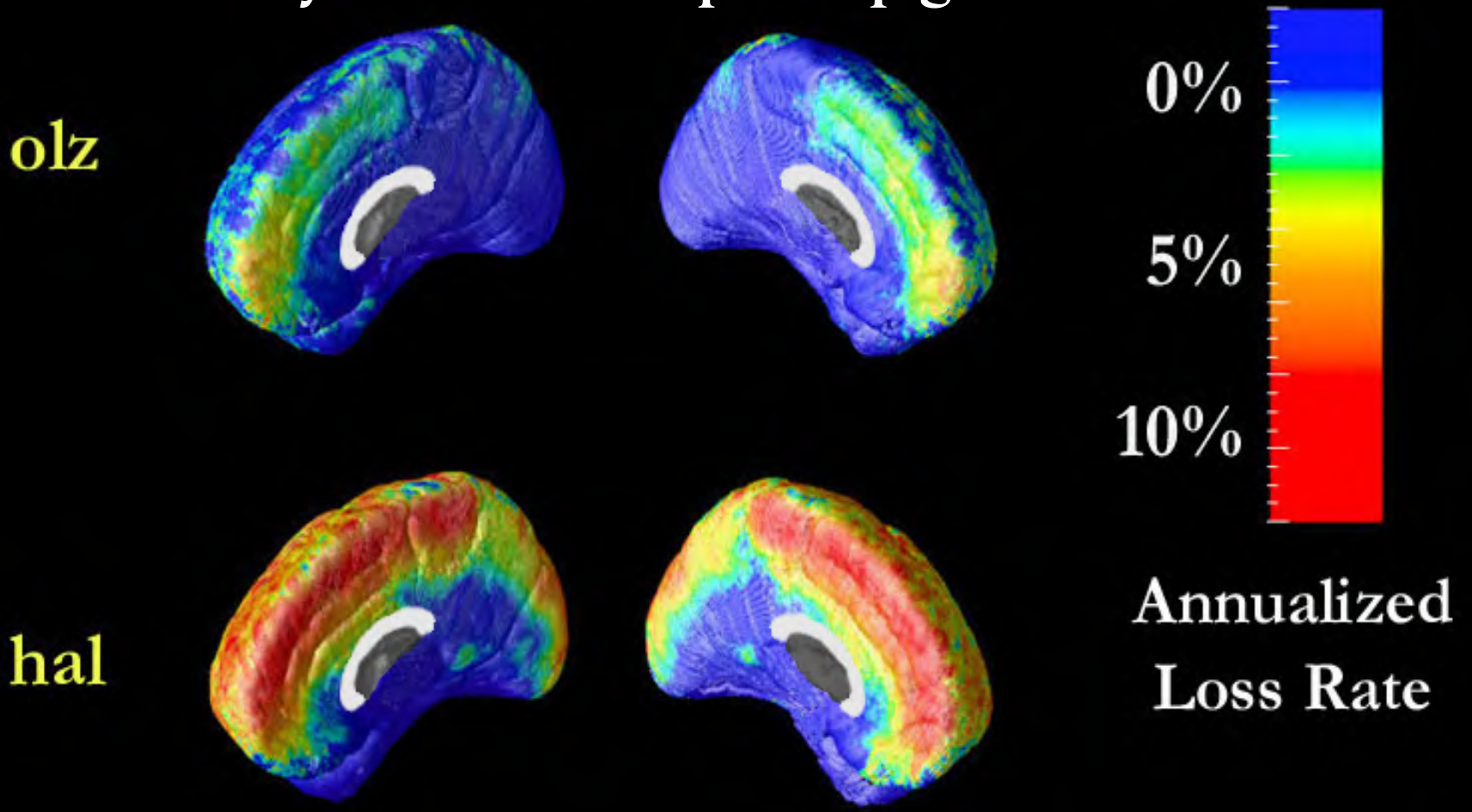
  - **genetic profiling** can empower drug trials (we do this now)

Discover **new drug targets**

What factors harm the brain? 1. Diseases, such as **Alzheimer's** – several commonly carried genes boost our risk for this (*ApoE4*: 3x; *CLU*, *CR1*, *PICALM*: 10-20% more risk each)

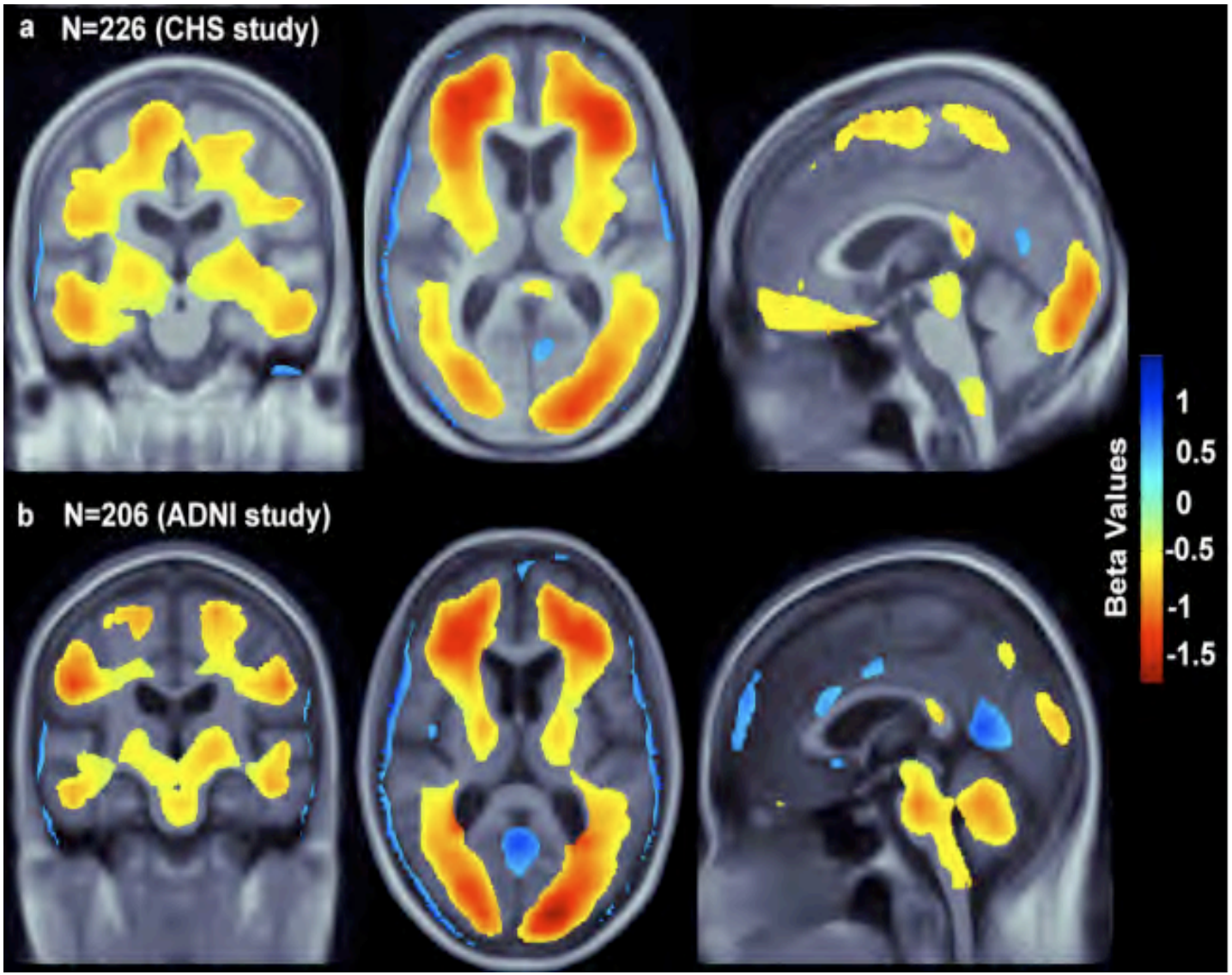


Imaging can pick up very subtle modulatory effects - Olanzapine Slows Gray Matter Loss; Imaging Reveals Differences; maybe it can also pick up gene effects



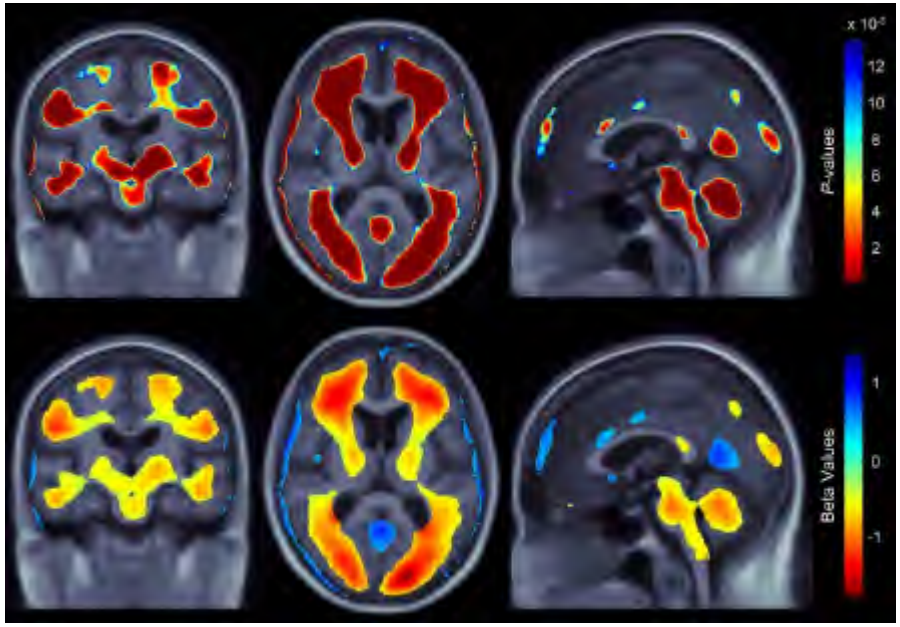
Thompson/Bartzokis/Lilly-HGDH Drug Trial/Lieberman 2008

‘Obese’ People have 8% more brain atrophy locally (N=432 MRI scans). Maps show % tissue deficit per unit gain in body mass index (BMI)

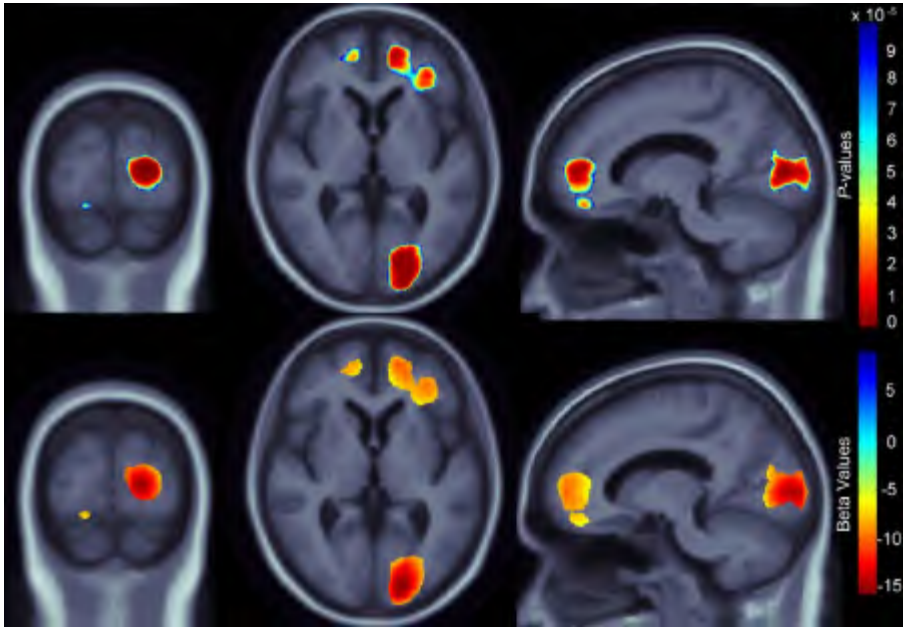


[1]Raji et al. Brain Structure and Obesity. *Human Brain Mapping, Aug. 2009.*

Geneticists discovered an “obesity susceptibility gene” (*FTO*) – surprisingly, we were able to pick up the effect of this common variant in brain images (Ho PNAS 2010)



BMI
(N=206 healthy elderly; corrected for multiple comparisons)



***FTO* association**
(N=206 healthy elderly; corrected for multiple comparisons)

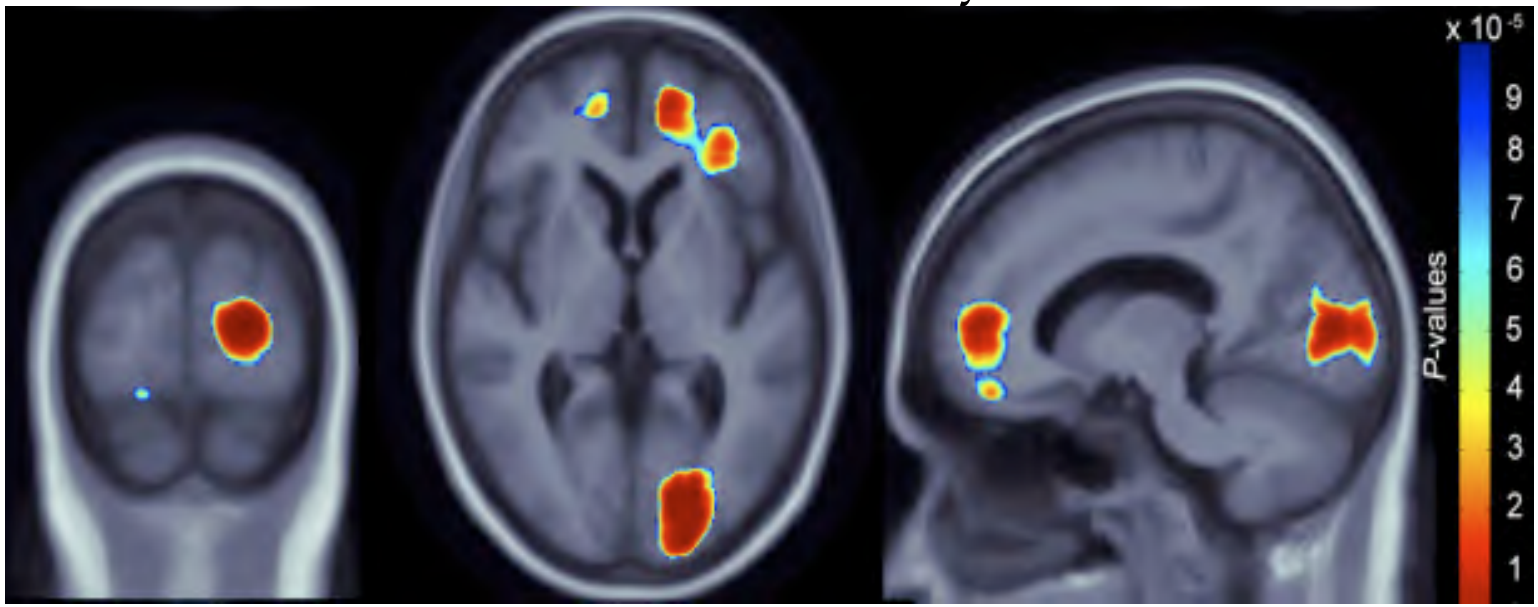
Obesity Risk Gene Carriers have Greater Brain Atrophy

46% of Western Europeans carry at least one adverse allele at this obesity risk locus, in *FTO* gene; for each 'bad' allele: gain 3 lbs, 1/2 inch waist circumference, crave ~200 more calories/day

They have a regional ~10% frontal lobe, ~15% occipital lobe deficit locally – regions with atrophy in people with higher BMI.

May be direct effect on brain, or mediated by BMI, or both

Significance Maps in *N*=206 normal subjects



April J. Ho[1*], Jason L. Stein[1*], Xue Hua PhD[1], Suh Lee[1], Derrek P. Hibar[1], Alex D. Leow MD PhD[1,2], Ivo D. Dinov PhD[1], Arthur W. Toga PhD[1], Andrew J. Saykin PsyD[3], Li Shen PhD[3], Tatiana Foroud PhD[4], Nathan Pankratz[4], Matthew J. Huentelman PhD[5], David W. Craig PhD[5], Jill D. Gerber[5], April N. Allen[5], Jason J. Corneveaux[5], Dietrich A. Stephan[6], Bryan M. DeChairo PhD[7], Steven G. Potkin MD[8], Clifford R. Jack Jr MD[9], Michael W. Weiner MD[10,11], Cyrus A. Raji PhD[12,13], Oscar L. Lopez MD[17], James T. Becker PhD[14-16], Owen T. Carmichael PhD[18], Charles S. DeCarli MD[19], Paul M. Thompson PhD[1,*], and the ADNI (2010). **Commonly carried allele within *FTO*, an obesity-associated gene, relates to accelerated brain degeneration in the elderly, PNAS 2010.**

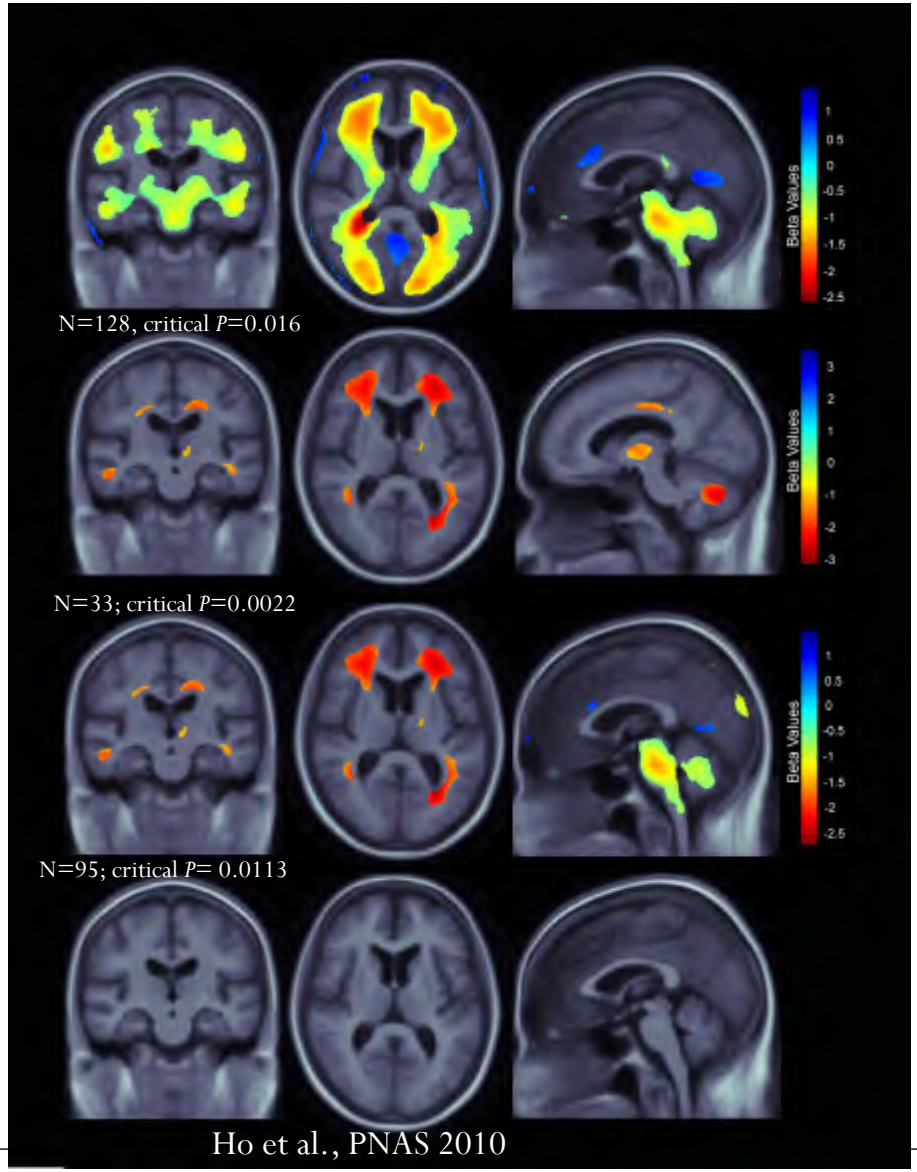
Depending on your *FTO* genotype, BMI may affect you in a different way

1 or 2 risk alleles

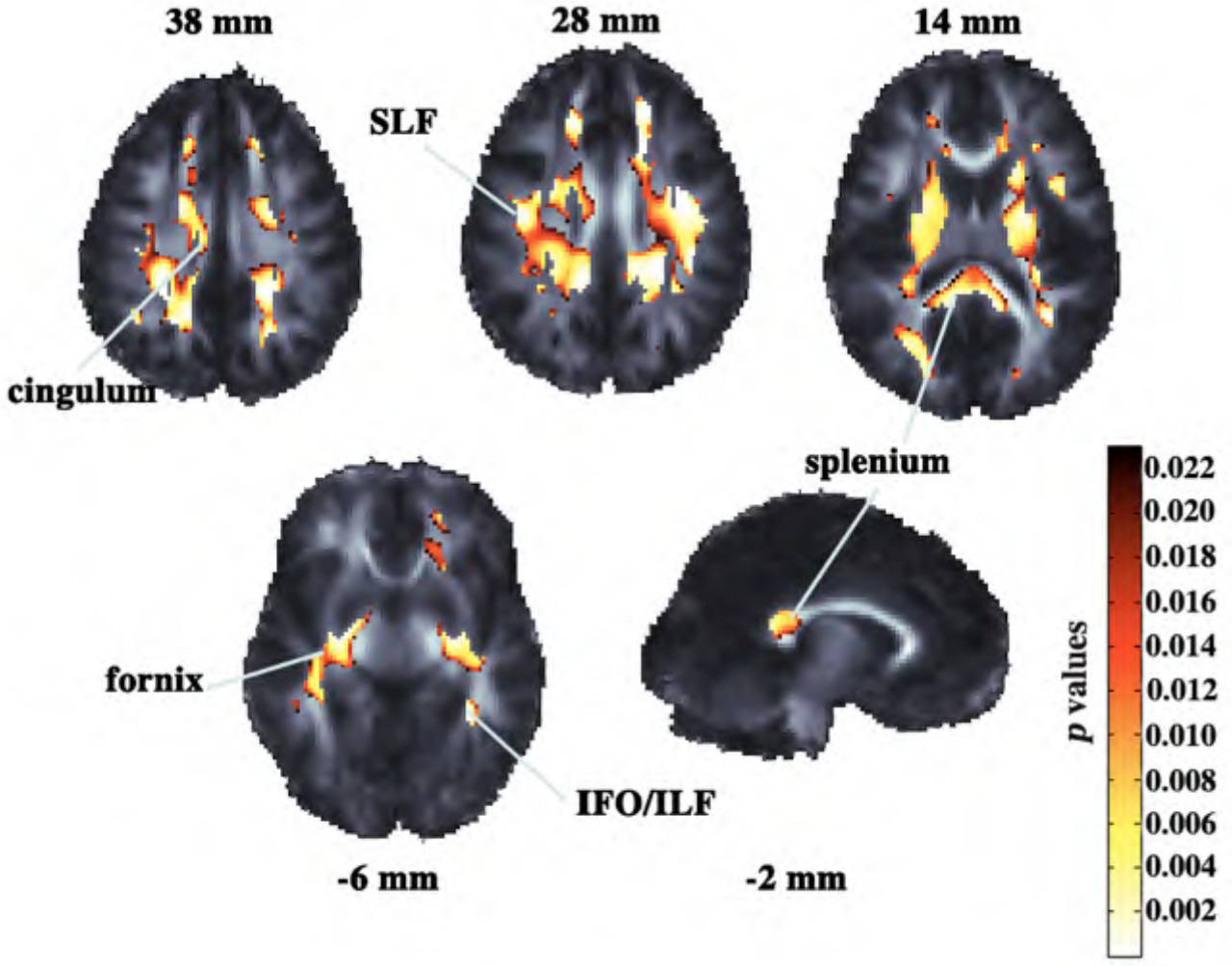
2 risk alleles

1 risk allele

*Does not pass FDR at 5% in non-carriers (N=78)



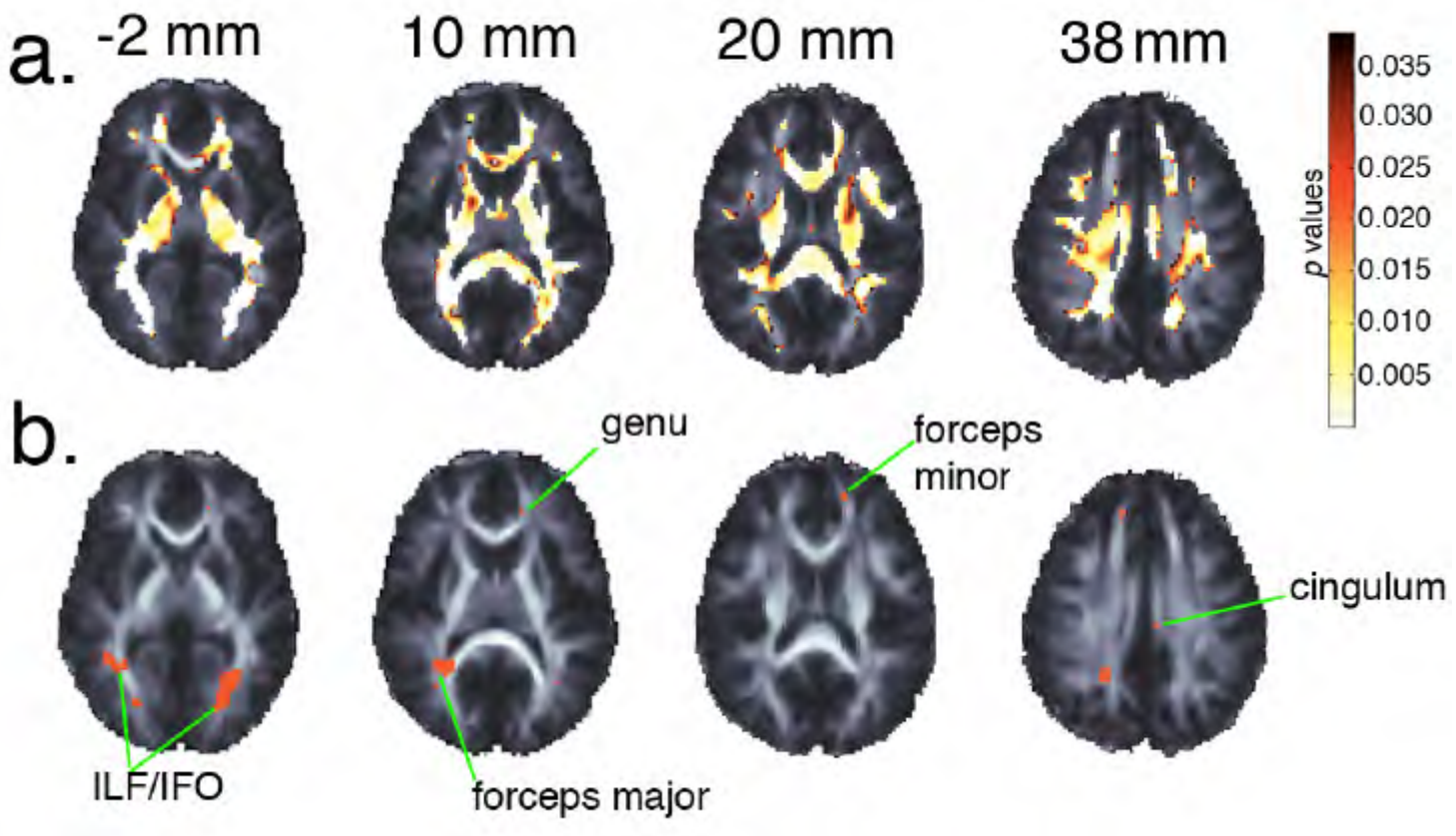
Alzheimer's risk gene carriers (*CLU*-C) have lower fiber integrity even when young (N=398), 50 years before disease typically hits [News covered in 20 countries]



Voxels where *CLU* allele C (at rs11136000) is associated with lower FA after adjusting for age, sex, and kinship in 398 young adults (68 T/T; 220 C/T; 110 C/C). FDR critical $p = 0.023$. Left hem. on Right

Braskie et al., Journal of Neuroscience, May 4 2011

Effect is even stronger for carriers of a schizophrenia risk gene variant, *trkA-T* (N=391 people)

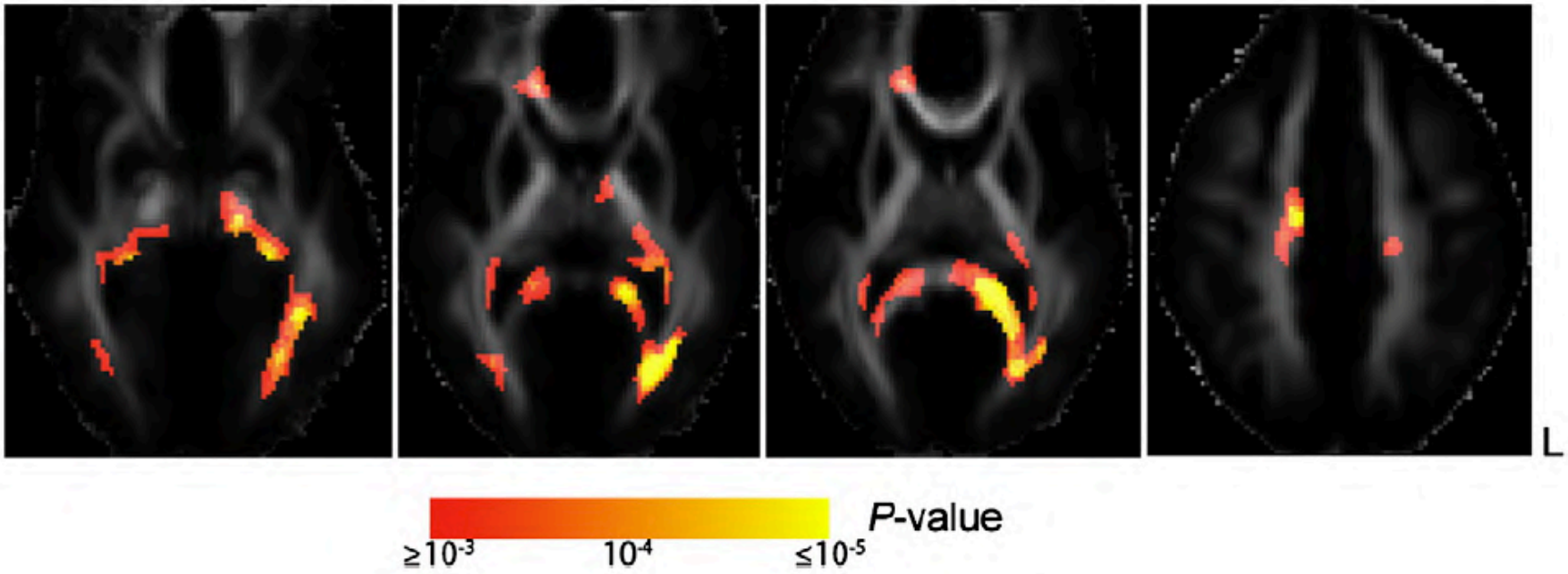


a. *p* values indicate where *NTRK1* allele T carriers (at rs6336) have lower FA after adjusting for age, sex, and kinship in 391 young adults (31 T+; 360 T-).
FDR critical *p* = 0.038.

b. Voxels that replicate in 2 independent halves of the sample (FDR-corrected). Left is on Right.

Braskie et al., Journal of Neuroscience, May 2012

…*also found for BDNF* gene (N=455 people). This is a well-known growth factor gene. Has been associated with working memory.

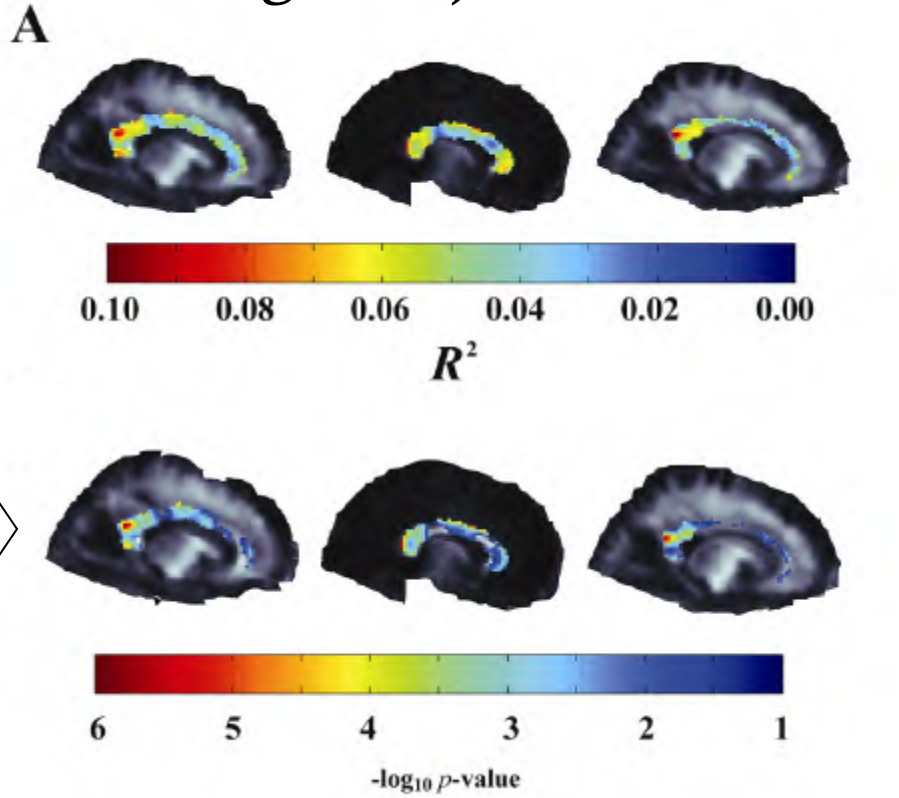


Can we use these discoveries to **develop a genetic test to help predict your brain integrity?**

To some extent yes. Use a **polygenic prediction model** based on all these SNPs.

We developed a polygenic test that can **predict a small proportion of the variance in brain integrity** (7 SNPs) and rate of brain loss (empower drug trials)

Neuro-chemical genes	*COMT*
	NTRK1
Neuro-developmental genes	*ErbB4*
	BDNF
Neuro-degenerative risk genes	*HFE*
	CLU



A significant fraction of variability in white matter structure of the corpus callosum (measured with DTI) is predictable from SNPs;

Holds up in independent, non-overlapping samples.

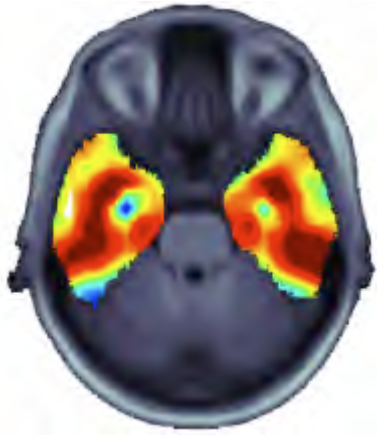
Kohannim O, *et al*. Predicting white matter integrity from multiple common genetic variants. *Neuropsychopharmacology* 2012, in press.

Brain measures are arguably* a good target for genetic analysis – may be easier to find genetic variants that directly affect the brain

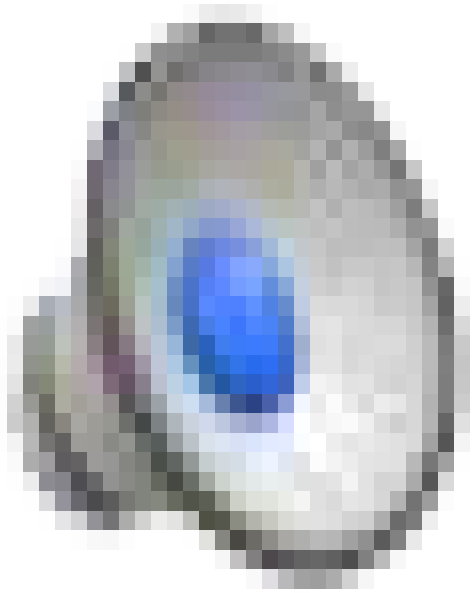
difficult

May require 10,000-30,000 people
e.g., the Psychiatric Genetics Consortium studies

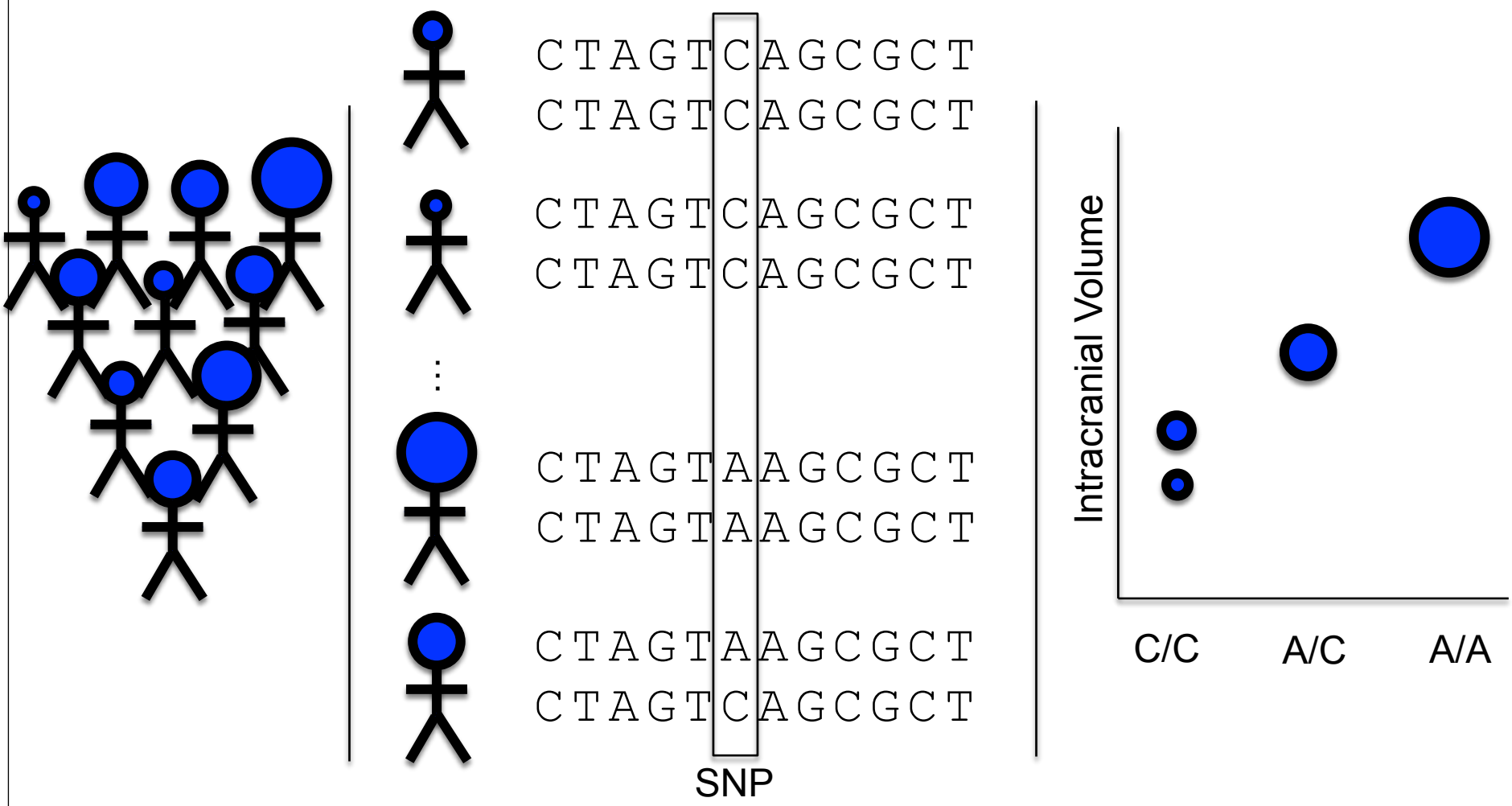
easier?



Gene variants may affect brain measures directly, many brain measures relate to disease status, they can be precisely and reproducibly measured



Finding Genetic Variants Influencing Brain Structure

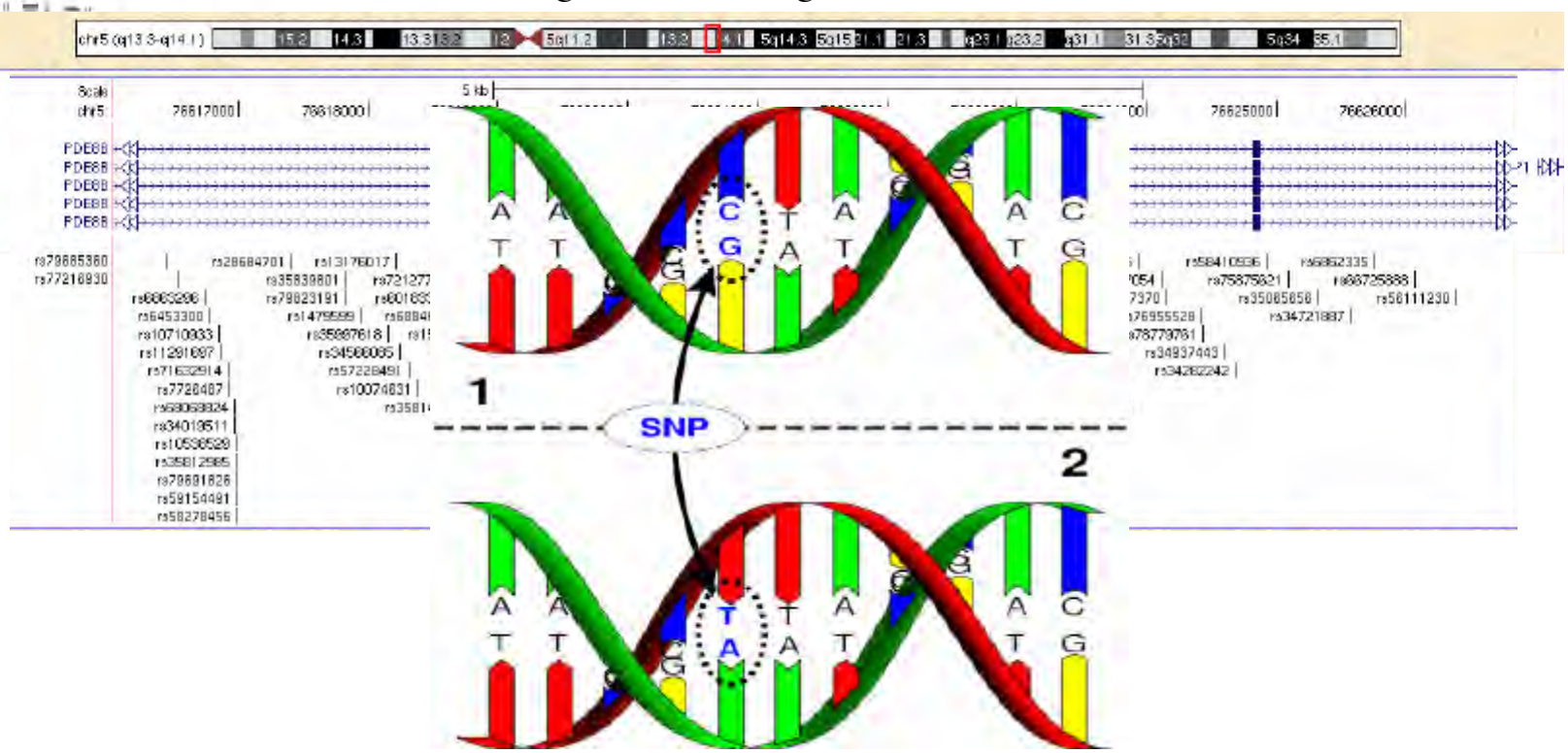


What do genome wide association studies (GWAS) try to find?

- common genetic ***variants*** related to a brain measure, or a disease, or a trait such as obesity, found by searching the genome

99.9% of DNA is the same for all people - DNA **variation** causes changes in height, personality, predisposition to disease, and brain structure.

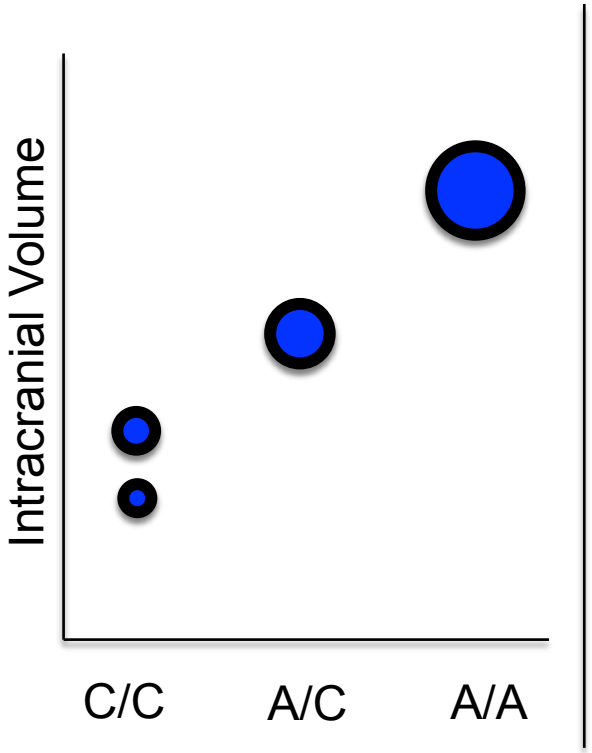
One type of variation is a single nucleotide polymorphism (SNP)
- Single letter change in the DNA code



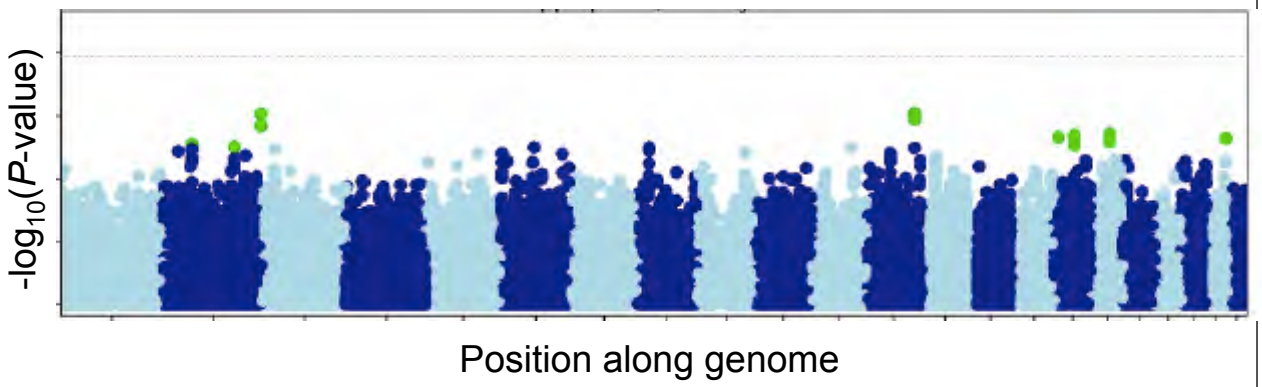
Single Nucleotide Polymorphism (SNP)

Genome-wide Association Study

One SNP
"Candidate gene" approach
e.g., *BDNF*



Screening
500,000 SNPs – 2,000,000 SNPs

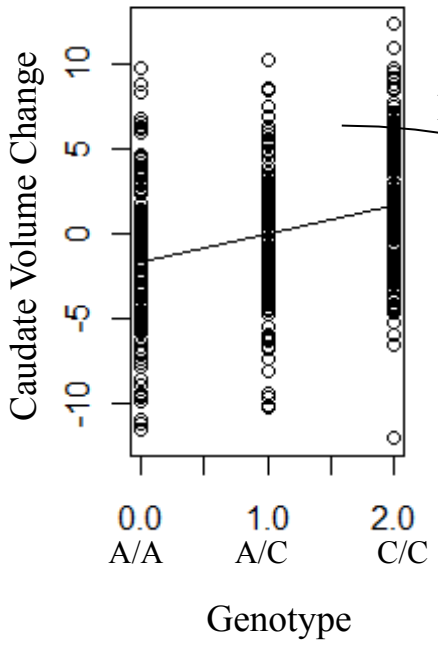


An unbiased search to find where in the genome a variant is associated with a trait.

Genome-wide association study

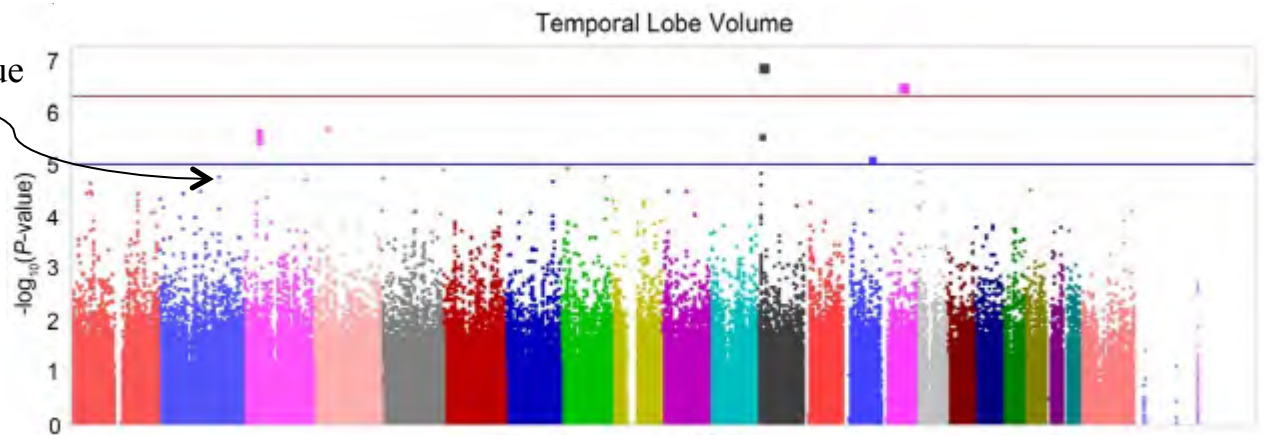
Which genomic variants are associated with a trait?

One SNP



P-value

500,000 to 2 million SNPs



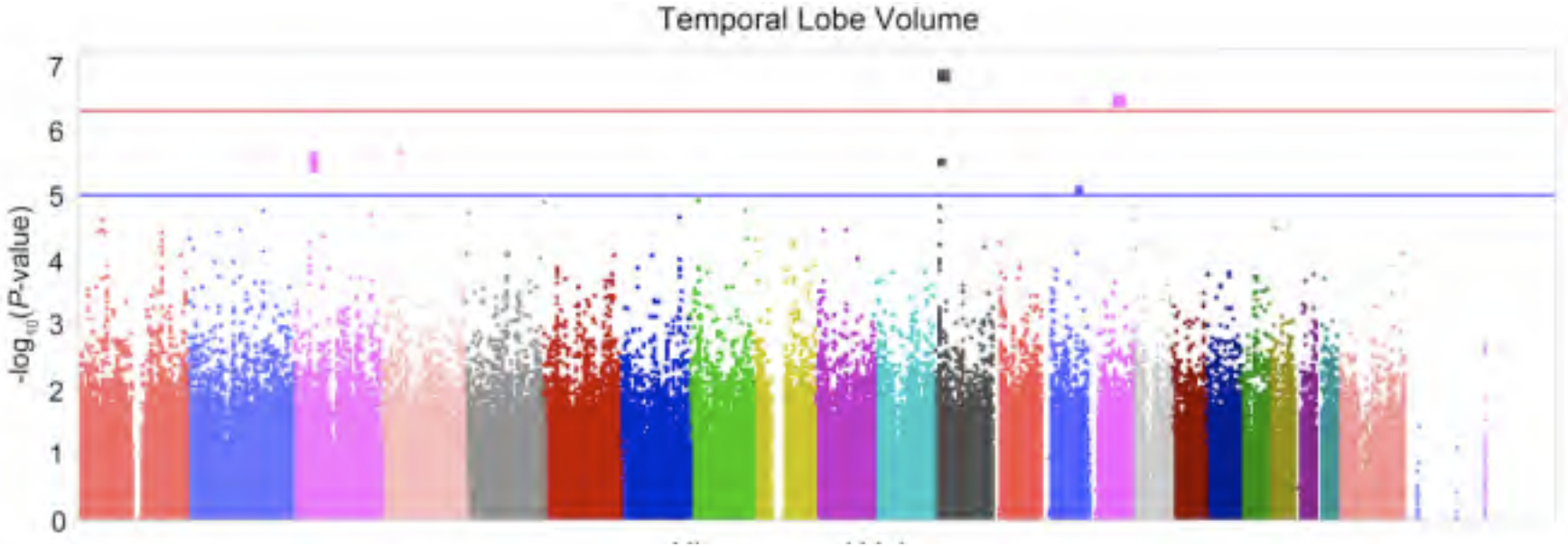
You hope to find a statistical association that is stronger than 20 million to 1, as you are testing so many SNPs

Usually need large samples (20,000 people)

GWAS = Finding common variants that explain some of the variation in a trait.

First Genome-Wide Screens of Brain Images (2009-2010)

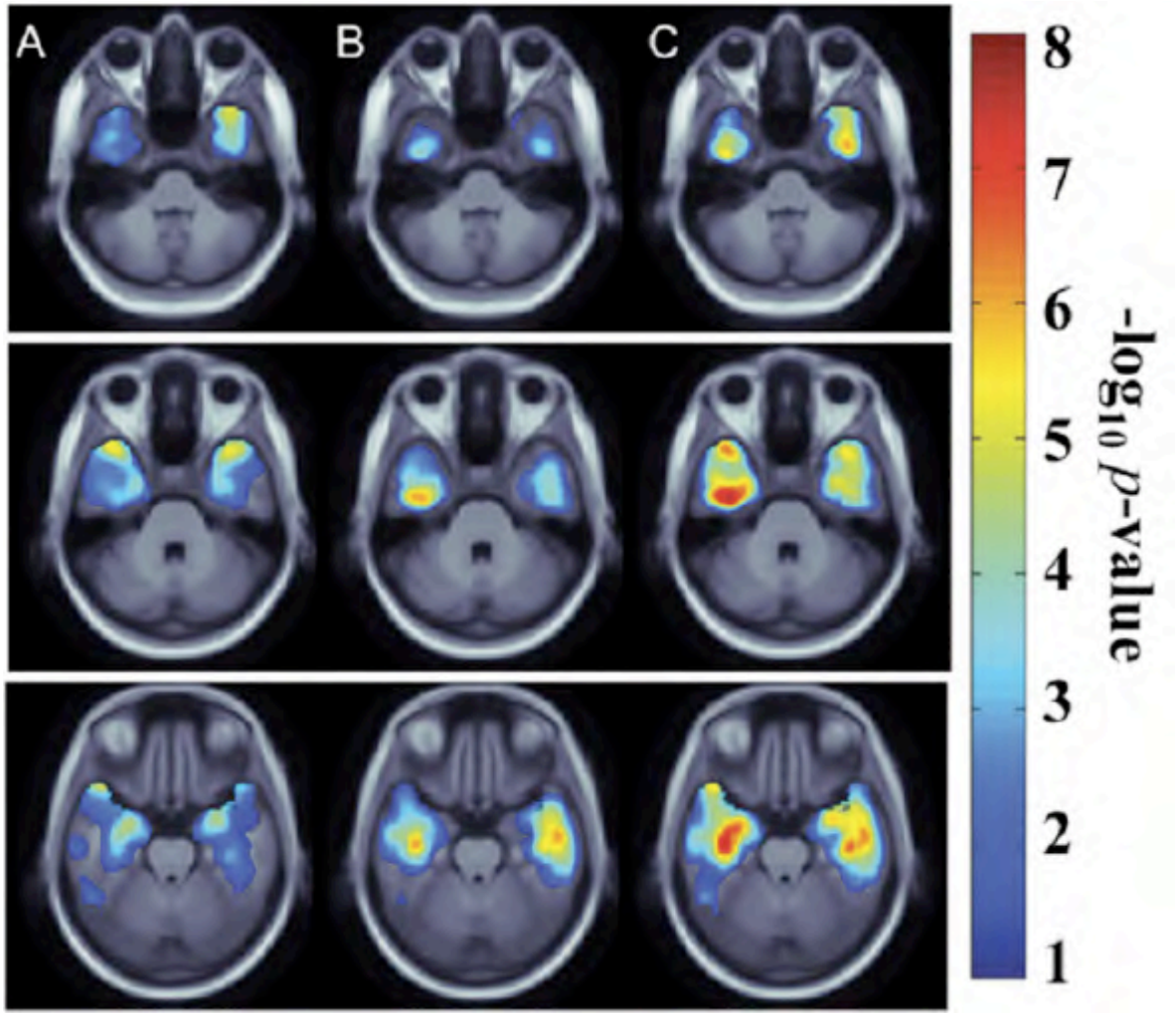
GRIN2b genetic variant was suggestively associated with 2.8% temporal lobe volume deficit; this was later replicated in a non-overlapping cohort
The NMDA-type glutamate receptor is a target of memantine therapy; first detected with GWAS in **N=742 subjects from the ADNI cohort**



GRIN2b is over-represented in AD
- could be considered an Alzheimer's disease risk gene
- needs replication

Jason L. Stein[1], Xue Hua PhD[1], Jonathan H. Morra PhD[1], Suh Lee[1], April J. Ho[1], Alex D. Leow MD PhD[1,2], Arthur W. Toga PhD[1], Jae Hoon Sul[3], Hyun Min Kang[4], Eleazar Eskin PhD[3,5], Andrew J. Saykin PsyD[6], Li Shen PhD[6], Tatiana Foroud PhD[7], Nathan Pankratz[7], Matthew J. Huentelman PhD[8], David W. Craig PhD[8], Jill D. Gerber[8], April Allen[8], Jason J. Corneveaux[8], Dietrich A. Stephan[8], Jennifer Webster[8], Bryan M. DeChairo PhD[9], Steven G. Potkin MD[10], Clifford R. Jack Jr MD[11], Michael W. Weiner MD[12,13], Paul M. Thompson PhD[1,*], and the ADNI (2010). **Genome-Wide Analysis Reveals Novel Genes Influencing Temporal Lobe Structure with Relevance to Neurodegeneration in Alzheimer's Disease, NeuroImage 2010.**

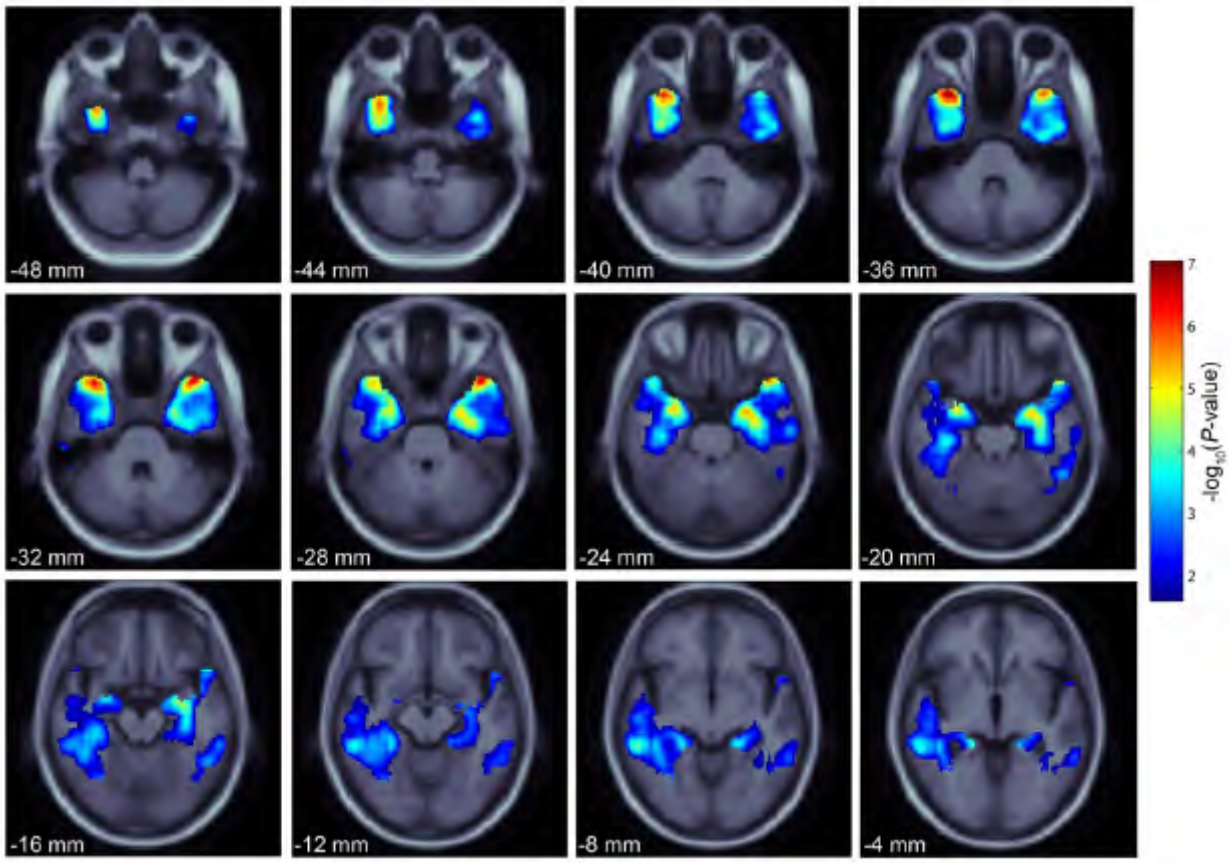
GRIN2b (glutamate receptor) genetic variant associates with brain volume in these regions; TT carriers have 2.8% more temporal lobe atrophy



Effect was later replicated in a younger cohort (Kohannim 2011)

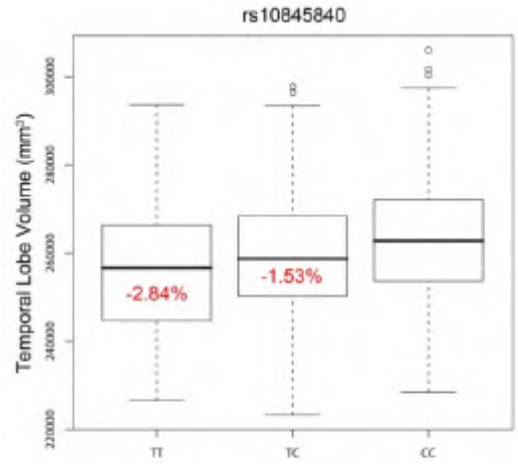
Jason L. Stein[1], Xue Hua PhD[1], Jonathan H. Morra PhD[1], Suh Lee[1], April J. Ho[1], Alex D. Leow MD PhD[1,2], Arthur W. Toga PhD[1], Jae Hoon Sul[3], Hyun Min Kang[4], Eleazar Eskin PhD[3,5], Andrew J. Saykin PsyD[6], Li Shen PhD[6], Tatiana Foroud PhD[7], Nathan Pankratz[7], Matthew J. Huentelman PhD[8], David W. Craig PhD[8], Jill D. Gerber[8], April Allen[8], Jason J. Corneveaux[8], Dietrich A. Stephan[8], Jennifer Webster[8], Bryan M. DeChairo PhD[9], Steven G. Potkin MD[10], Clifford R. Jack Jr MD[11], Michael W. Weiner MD[12,13], Paul M. Thompson PhD[1,*], and the ADNI (2010). **Genome-Wide Analysis Reveals Novel Genes Influencing Temporal Lobe Structure with Relevance to Neurodegeneration in Alzheimer's Disease, NeuroImage, 2010.**

Effect of carrying adverse SNP is ~1.4% lower volume per allele, same as ENIGMA's top SNP

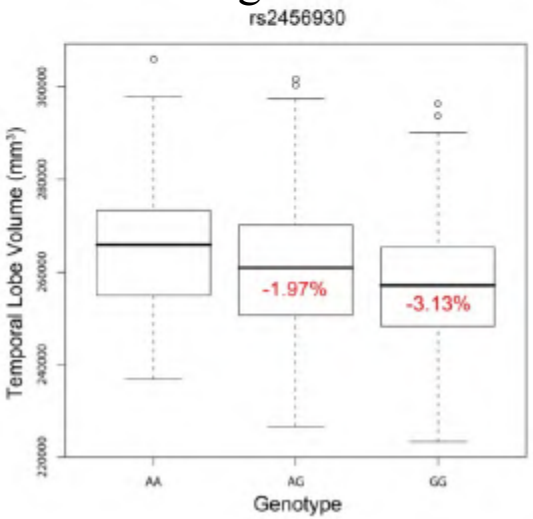


GRIN2B SNP (rs10845840)

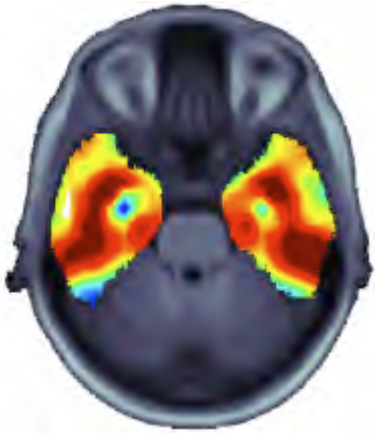
GRIN2B SNP



intergenic SNP



Brain measures are a good target for genetic analysis – common DNA variation affects them and they relate to disease status



STEP 2 – OUR STUDY FOUND THIS CONNECTION
***P* = 1.26x10^{-7}; later replicated**

Imaging Biomarker Related to Illness
Temporal Lobe Volume

STEP 1 – THIS CONNECTION WAS WELL-ESTABLISHED

P = 5.19x10^{-11}

Genetic Variation
GRIN2B
(rs10845840)

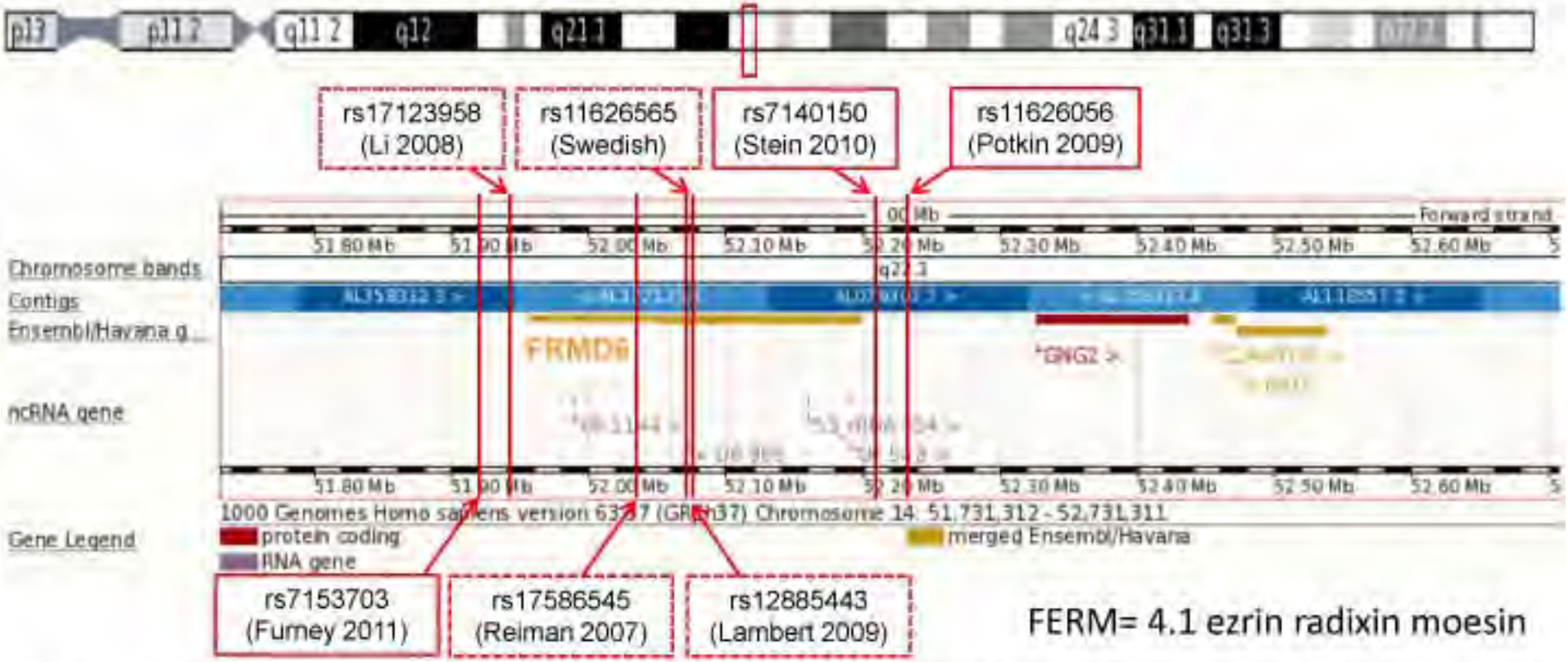
Diagnostic Status
Healthy elderly vs. AD or MCI

STEP 3 – CAN LATER CHECK IF IT IS ASSOCIATED WITH DISEASE, P = 0.039;
NEEDS REPLICATION

FRMD6: FERM domain-containing protein 6

Detected in 3 imaging genetics studies (2 ADNI; 1 ADNI/ANM) and validated by case/control GWAS

Chr 14q22.1



FERM= 4.1 ezrin radixin moesin

Hong et al, Genome-wide and gene-based association implicates FRMD6 in Alzheimer disease. Hum Mutat. 2011 Dec 20. [Epub].

Across the four combined GWAS samples, *FRMD6* showed the highest non-*APOE* signal: $p = 2.6 \times 10\text{-}14$).

Saykin, 12/27/11

Source	SNP	Position	MAF	p-value	OR (95%CI)
Stein 2010	rs7140150	51080549	0.4566	4.77 × 10-7	*n/a - Imaging QTL*
Potkin 2009	rs11626056	51303026	0.3295	1.18 × 10-6	*n/a - Imaging QTL*
Furney 2011	rs7153703	50989572	0.2130	3.38 x 10-6	*n/a - Imaging QTL*
Swedish	rs11626565	51143880	0.0599	2.45 x 10-5	1.69;1.34-2.13
Reiman 2007	rs17586545	51104768	0.0334	4.18 x 10-5	1.88; 1.36-2.54
Li 2008	rs17123958	51011874	0.1040	7.59 × 10-5	2.12; 1.38-3.24
Lambert 2009	rs12885443	51145403	0.1769	5.34 x 10-4	1.16; 1.07-1.25

FRMD6 gene story - Imaging Genetics can take the lead in uncovering disease-relevant genes

Novel candidate gene for AD
First recognized in several **imaging genetics analyses**
- **later replicated** in a **large case/control cohort**
- and by reanalysis of prior case/control GWAS data.

Furney et al phenotype was ventricular volume
Potkin et al was local hippocampal volume
Stein et al was a voxel-based map of regional brain volume differences.

Odds ratios for *FRMD6* SNPs from the 4 GWAS studies in Hong et al range from 1.16 to 2.12 - larger than most top AD genes (*Nature Genetics,* April 2011)
But still well below *APOE* (OR ~ 3).

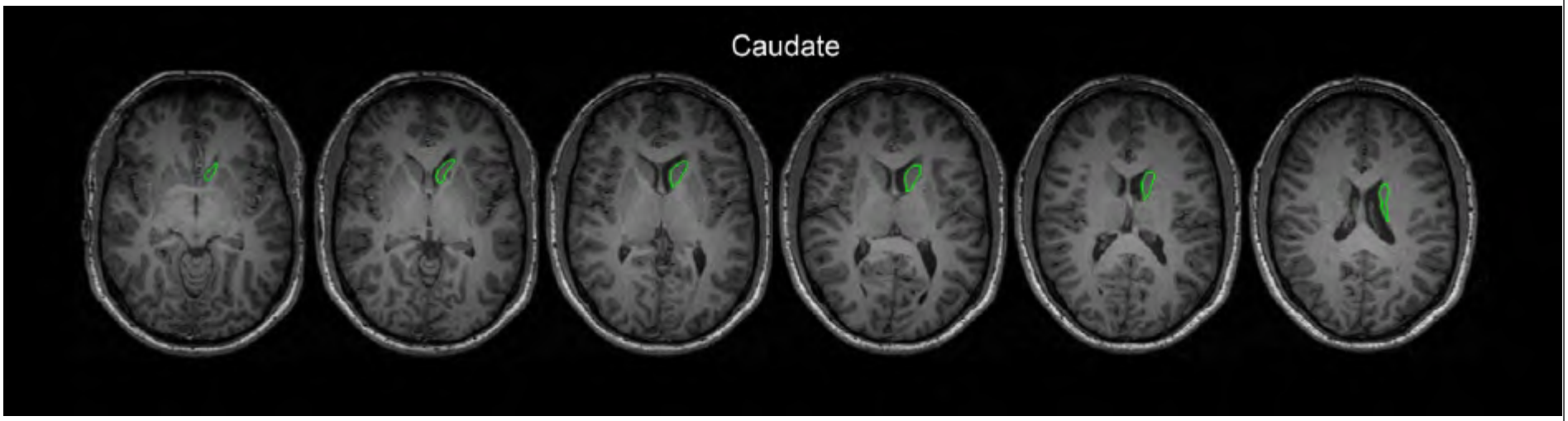
FRMD6 appears promising as a replicated candidate gene.
Little data so far on its biological function.

Jason L. Stein[1], Xue Hua PhD[1], Jonathan H. Morra PhD[1], Suh Lee[1], April J. Ho[1], Alex D. Leow MD PhD[1,2], Arthur W. Toga PhD[1], Jae Hoon Sul[3], Hyun Min Kang[4], Eleazar Eskin PhD[3,5], Andrew J. Saykin PsyD[6], Li Shen PhD[6], Tatiana Foroud PhD[7], Nathan Pankratz[7], Matthew J. Huentelman PhD[8], David W. Craig PhD[8], Jill D. Gerber[8], April Allen[8], Jason J. Corneveaux[8], Dietrich A. Stephan[8], Jennifer Webster[8], Bryan M. DeChairo PhD[9], Steven G. Potkin MD[10], Clifford R. Jack Jr MD[11], Michael W. Weiner MD[12,13], Paul M. Thompson PhD[1,*], and the ADNI (2010). **Genome-Wide Analysis Reveals Novel Genes Influencing Temporal Lobe Structure with Relevance to Neurodegeneration in Alzheimer's Disease, NeuroImage 2010.**

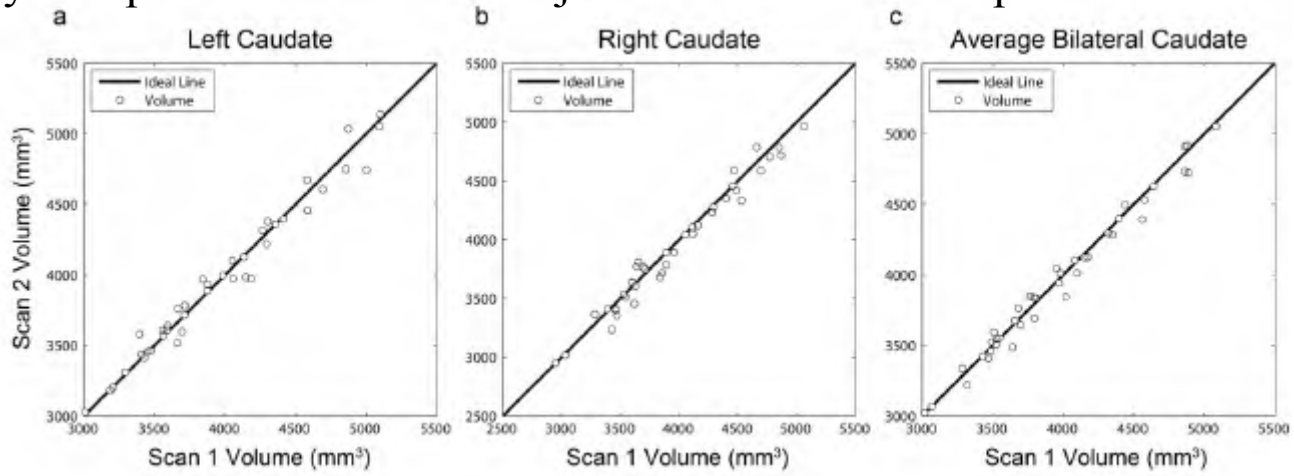
Beginnings of ENIGMA – 2 large populations; discover genes in one, then see if they replicate in the other

Study Name	Subjects	Genetic Information	Age/Sex Distribution
Alzheimer's Disease NeuroImaging Initiative (ADNI)	734 healthy elderly, MCI, and AD	Illumina 610K GWAS	75.5 ± 6.8 years 432 male/302 female
Brisbane Adolescent/ Young Adult Longitudinal Twin Study (BLTS)	464 young healthy MZ/DZ twins (239 families)	Illumina 610K GWAS	23.7 ± 2.1 years 188 male/276 female

Finding the Caudate Nucleus Automatically in 1198 MRI Scans – we can measure its volume reliably



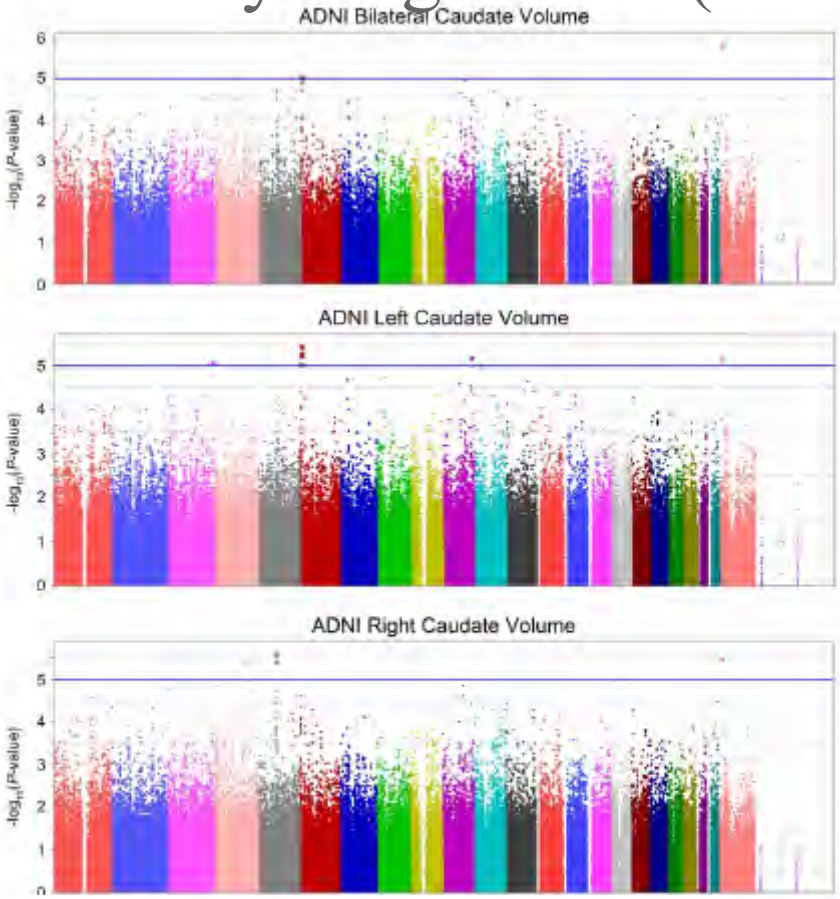
Reliability in repeated scans of 40 subjects – same answer if person is scanned again



ICC = 0.986 ICC = 0.985 ICC = 0.990

Stein JL, Derrek P. Hibar[1], Sarah K. Madsen[1], Mathew Khamis[1], Katie L. McMahon[2], Greig I. de Zubicaray[3], Narelle K. Hansell[4], Grant W. Montgomery[4], Nicholas G. Martin[4], Margaret J. Wright[4], Andrew J. Saykin[5], Clifford R. Jack, Jr[6], Michael W. Weiner[7,8], Arthur W. Toga[1], Paul M. Thompson[1,] and the Alzheimer's Disease Neuroimaging Initiative* (2011). **Discovery and replication of dopamine-related gene effects on caudate volume in young and elderly populations (N=1198) using genome-wide search,** ***Molecular Psychiatry,*** 16: 927-937, **September 2011.**

Caudate association peak in *PDE8B* gene, replicates in 2nd young cohort (N=1198 people total)

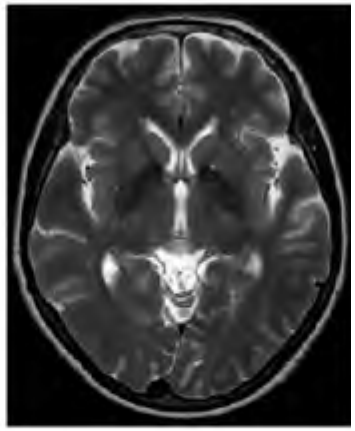


Same Gene implicated in Autosomal Dominant -Striatal Degeneration - Very severe effect on Caudate volume

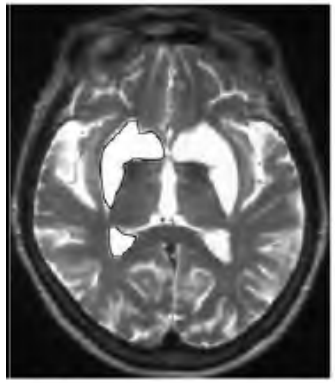
-In healthy people, affects Caudate volume

-Phosphodiesterase = key protein in the dopamine signaling cascade

-still not GW-significant in any one cohort alone



Control

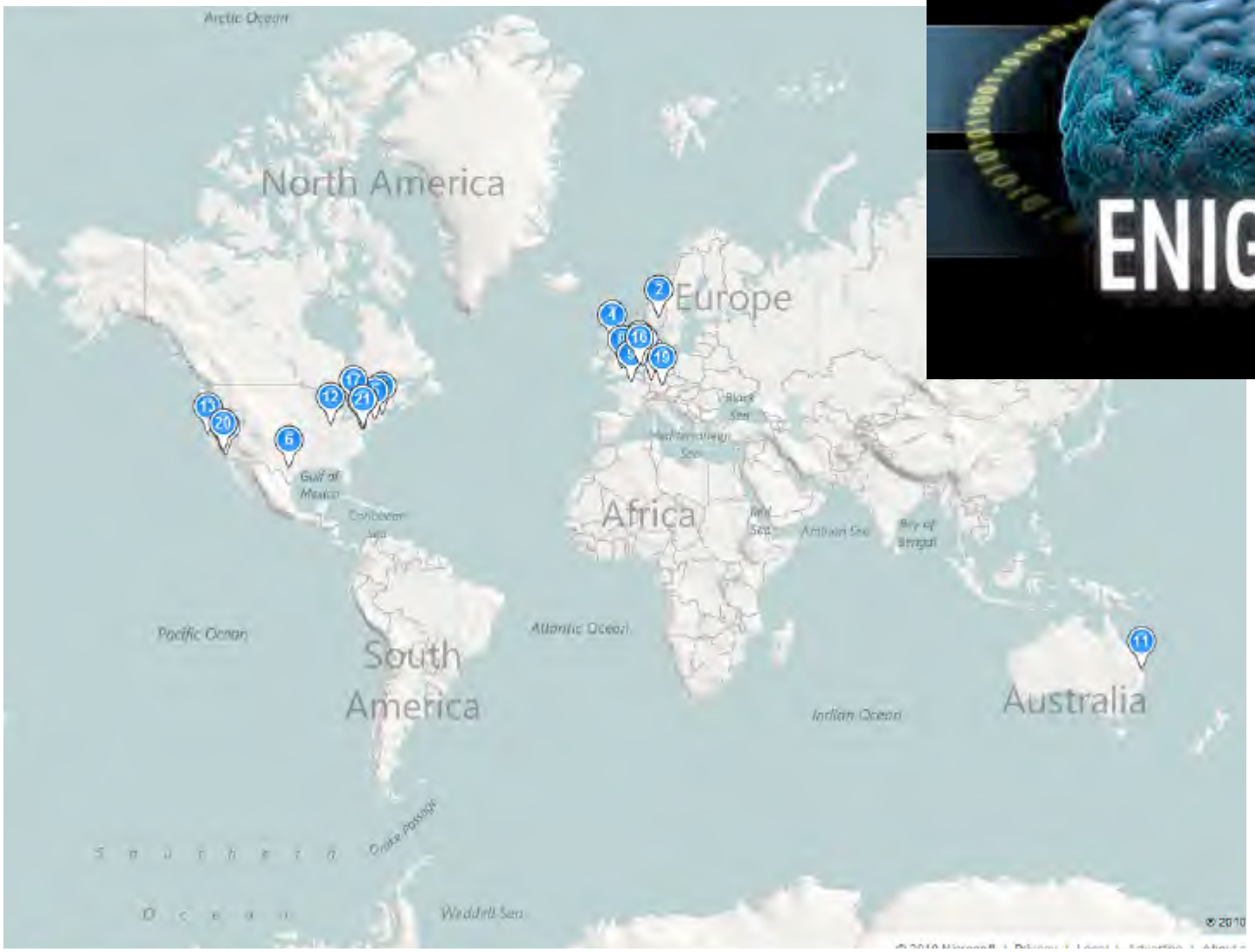


ADSD patient

				ADNI							BLTS					
Chr	SNP	Position	Gene	A1	Freq	N	β	SE	*P*	*P* | *diag*	A1	Freq	N	β	SE	*P*
Right Caudate																
5	rs153030	76817227	*WDR41*	A	0.499	731	147.4	31.0	2.36×10^{-6}	6.00×10^{-6}	C	0.524	462	-83.2	33.2	0.012
5	rs163035	76815798	*WDR41*	T	0.499	734	147.2	31.0	2.47×10^{-6}	6.00×10^{-6}	G	0.524	461	-83.2	33.2	0.013
5	rs335636	76760355	*PDE8B*, *WDR41*	A	0.500	733	143.8	30.9	3.90×10^{-6}	8.00×10^{-6}	G	0.525	464	-81.1	33.0	0.014
4	rs1299288	132606407		G	0.230	734	-169.4	36.6	4.43×10^{-6}	5.00×10^{-6}	T	0.770	464	-42.0	39.3	0.286

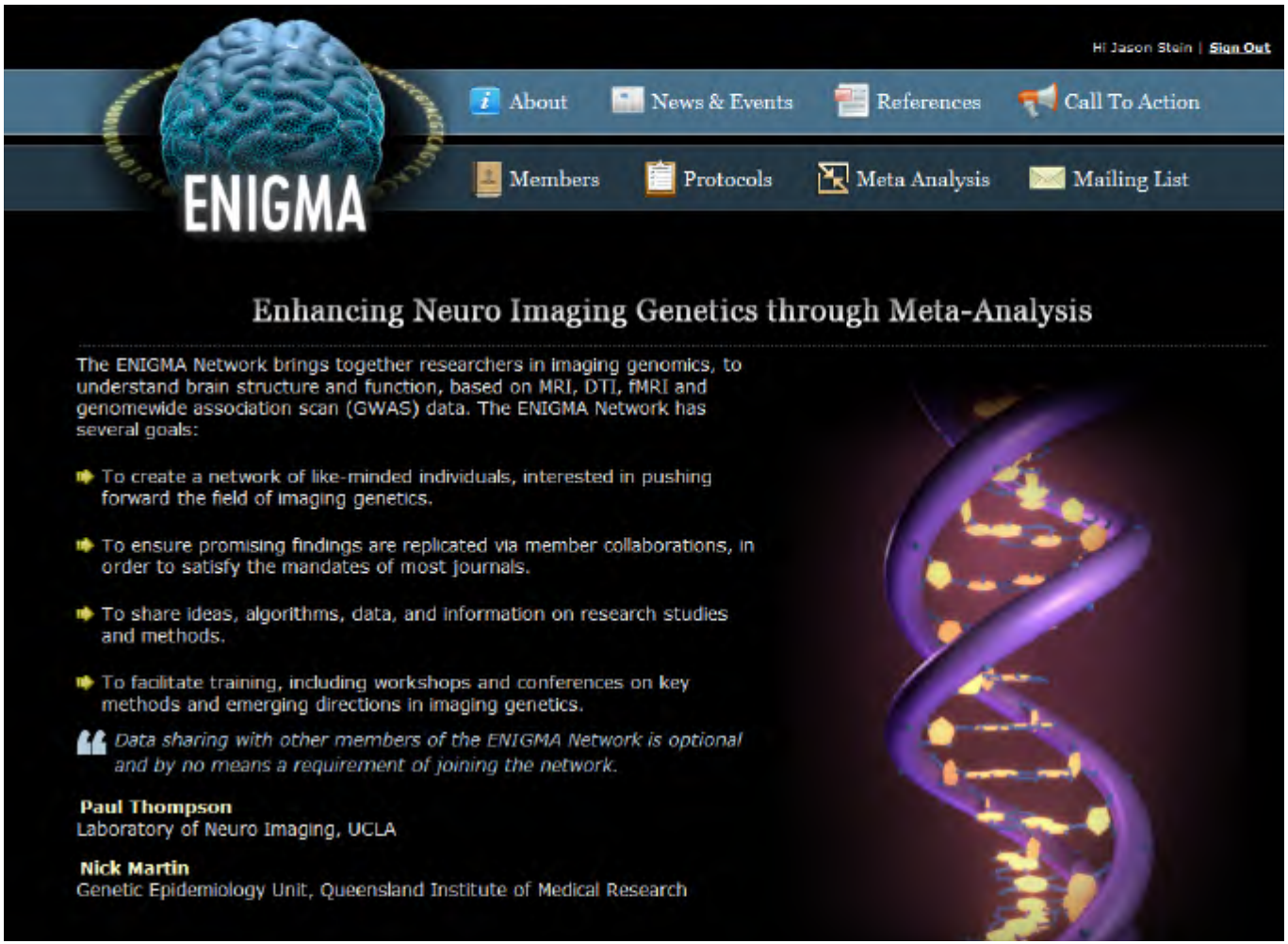
Initial Creation of the ENIGMA Consortium

Many sites were collecting MRI and DNA
– needed each other for replication



Replication through collaboration

http://ENIGMA.loni.ucla.edu



- **>200 scientists, 12 countries; must have DNA and MRI scans**
- **Many new members joining, several Working Groups**

Meta-Analysis – each site uploads its genome-wide scans
- see if any of 500,000+ common genetic variants affect brain volume, brain integrity on DTI, brain amyloid measured with PET
- each site's "vote" depends on how many subjects they assessed

Submissions

Group ID	Project Name	Contact Person	Meta-Analysis	File Status
44	GOBS	John Blangero	INFO	STATUS
78	Max Planck Institute of Psychiatry, Munich	Philipp Sämann	INFO	STATUS
83	MGH / Genomic SuperStructure	Randy Buckner / Jordan Smoller	INFO	STATUS
88	Imagen	Roberto Toro	INFO	STATUS
94	QTwin	Jason Stein/Sarah Medland	INFO	STATUS
101	Norwegian Cognitive Neurogenetics	Thomas Espeseth	INFO	STATUS
105	Roel Ophof f- UCLA/UMC Utrecht	Kristel van Eijk	INFO	STATUS
108	ADNI	Li Shen	INFO	STATUS
113	LBC1936	Lorna Lopez	INFO	STATUS
114	BIG Study	Barbara Franke/Alejandro Arias	INFO	STATUS
148	NESDA	Saskia Woudstra	INFO	STATUS
149	MooDS	Andreas Meyer-Lindenberg	INFO	STATUS
151	fBIRN	Theo G.M. van Erp	INFO	STATUS
161	Thematic Organized Psychosis Research (TOP)	Ole Andreassen	INFO	STATUS
164	NIMH-IRP	Francis McMahon	INFO	STATUS

Total Subject Tally

N w/ Patient	N w/o Patients
6,496	4,716

Genetic Imputation – allows ENIGMA members to compare and combine their data

Differences in genotyping chips used require
imputation to the same reference sample
so each group is studying the same SNPs.

Imputation is similar to resampling in imaging – put everything on the same grid
ENIGMA1 – HapMap reference panel
ENIGMA2 – "1000 Genomes" (1KG) reference panel;
Use imputation protocol on ENIGMA website

Sites had to measure regional brain volumes from MRI with validated, automated software programs (e.g., Freesurfer, FSL; some sites ran both; there was extensive QC, outliers left in if visually verified)

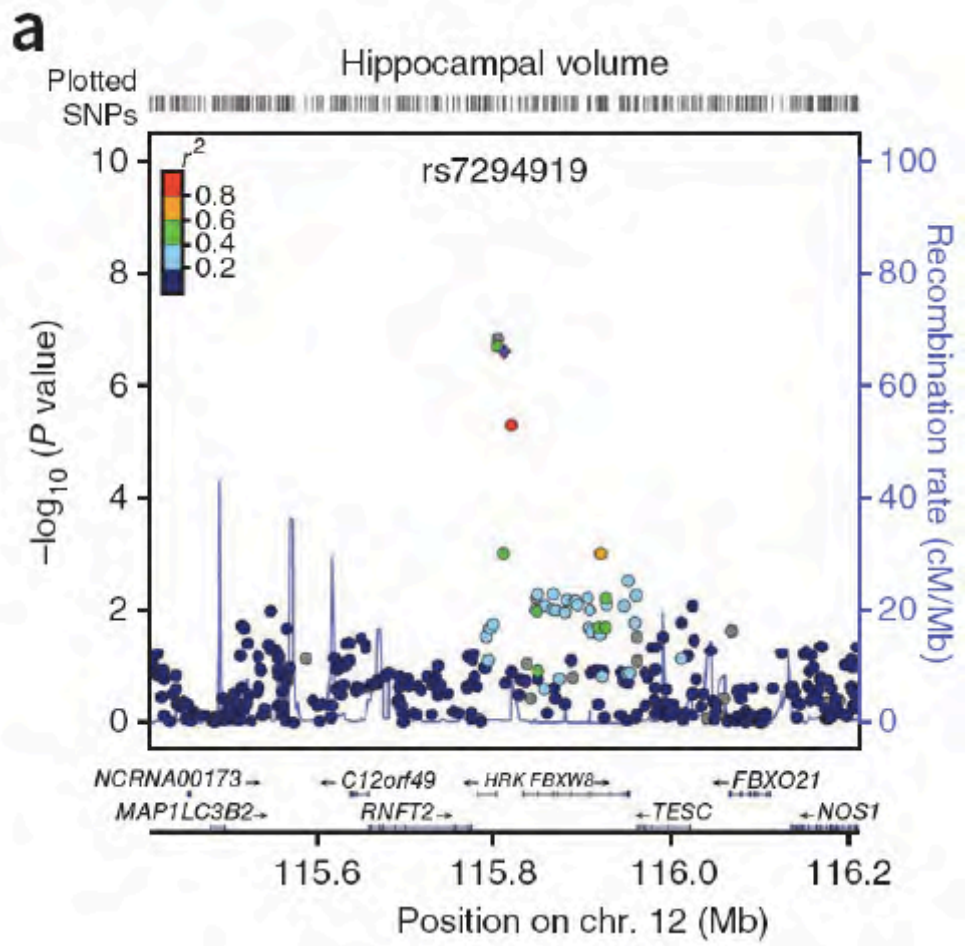
	Hippocampus		Brain Volume		ICV	
Study Name	***r***	**N**	***r***	**N**	***r***	**N**
ADNI	0.87	657	0.67	657	0.94	657
BFS	0.84	215	0.84	215	0.82	215
BIG	0.72	2180	0.97	927	0.72	927
fBIRN	0.70	78	0.75	78	0.87	78
IMAGEN	0.72	518	0.93	518	0.91	518
MooDS	0.72	137	N/A	N/A	N/A	N/A
NCNG	0.63	327	0.96	327	0.97	327
QTIM	0.71	386	0.93	386	0.73	386
SHIP	0.86	24	0.96	24	0.93	24
SHIP-TREND	0.68	24	0.98	24	0.91	24
TOP	0.71	419	0.97	419	0.94	419
UMCU	0.61	181	N/A	N/A	N/A	N/A
EPIGEN	0.78	203	N/A	N/A	N/A	N/A
GOBS	0.76	724	0.99	726	0.94	726
NIMH-IRP	0.53	20	0.91	20	0.94	20
COMBINED	0.75	6093	0.95	4321	0.90	4321

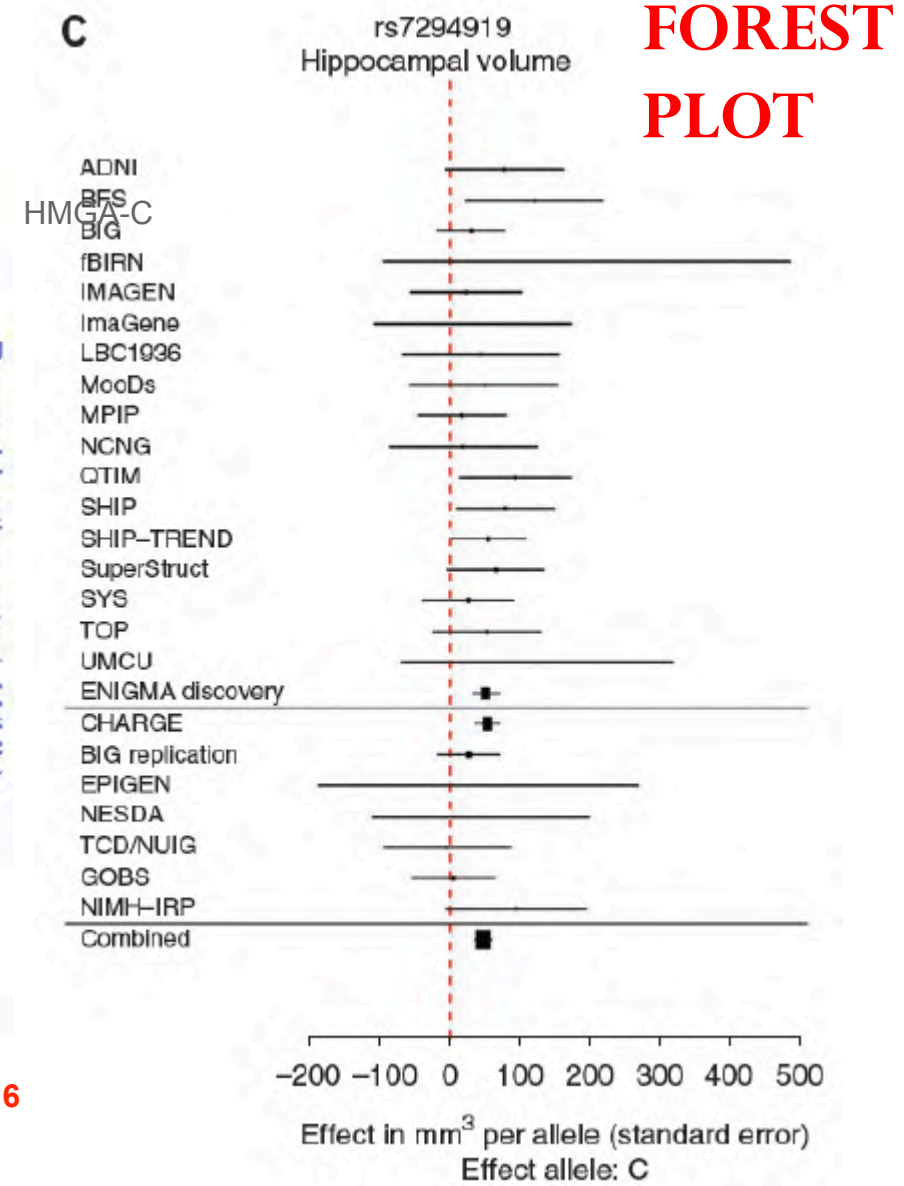
The **correlation between software programs** is comparable to human interrater variability (ICC=0.75-0.95); important in deciding **which structures to prioritize**

(Stein, Medland, Vasquez, Hibar, et al., *Nature Genetics*, 2012)

4 Nature Genetics papers (April 15 2012) - largest brain imaging studies in the world
Chromosome 12 variant in *HMGA2* boosts brain volume by 9cc, IQ by 1.3 points
HP volume SNP ~ 3 years of aging,
Assoc. with 1.2% decrease in vol per allele

FOREST PLOT

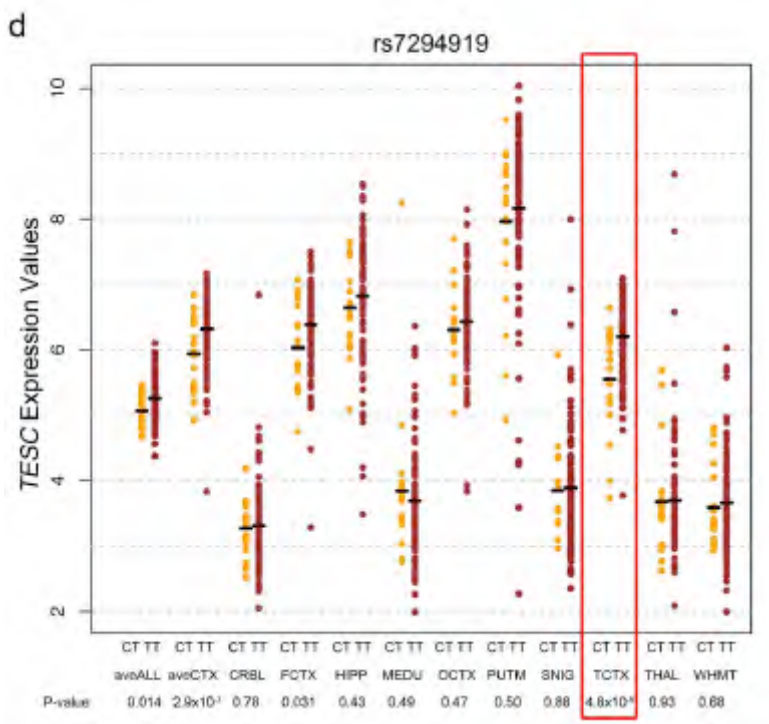




After Replication: **N = 21,151**; *P* = 6.7 **x 10^{-16}**

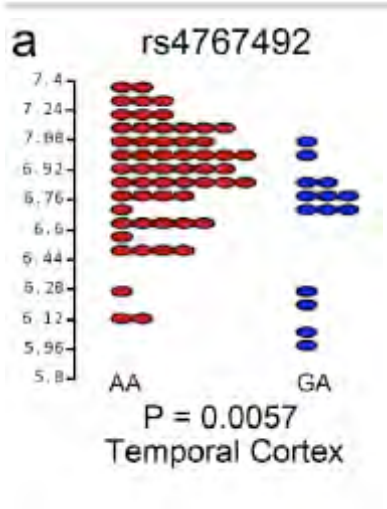
(Stein, Medland, Vasquez, Hibar **+ 207 authors**, *Nature Genetics*, 2012)

The hippocampal volume SNP (or the closest available proxy) was associated with differences in the expression of a nearby gene, *TESC, in brain tissue*

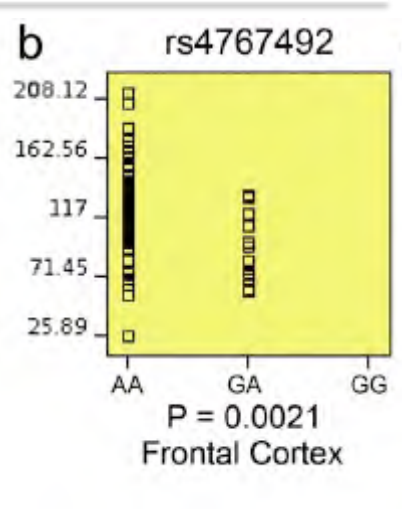


UK Brain Expression Database

Proxy SNP



UCL Epilepsy Cohort



SNPExpress Database

(Stein, Medland, Vasquez, Hibar **+ 207 authors**, *Nature Genetics*, 2012)

Previously Studied Candidate Genes

Gene	SNP (proxy)	P-value	Het. P-value
Full Discovery sample – including patients			
BDNF	rs6265	0.969	0.375
TOMM40	rs2075650	**0.034**	2.31×10^{-5}
CLU	rs11136000	0.287	0.186
PICALM	rs3851179	0.079	0.035
ZNF804A	rs1344706	0.325	0.908
COMT	rs4680	0.211	0.827
DISC1	rs821616 (rs1754606 r^2=1.00)	0.940	0.240
NRG1	rs35753505 (rs12681411 r^2=0.835)	0.636	0.116
DTNBP1	rs1011313	0.416	0.832
DTNBP1	rs1018381 (rs875463 r^2=1.00)	0.882	0.431

Previously studied candidate polymorphisms **showed little association** to hippocampal volume; Het. P-value – tests for heterogeneity of allele frequency across cohorts; some cohorts include AD patients

HMGA2 gene, Brain Size, and IQ

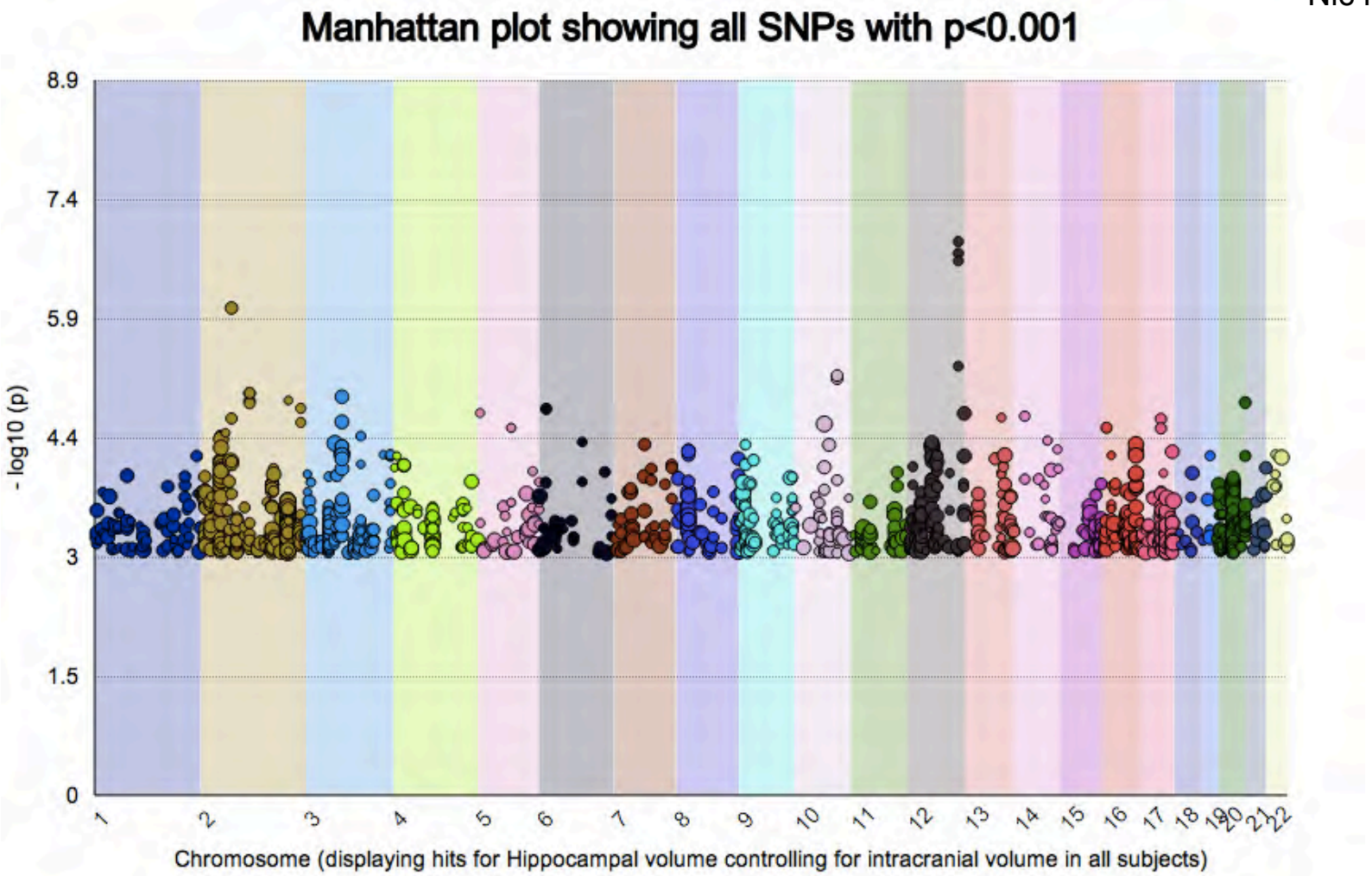
- Carriers of the C allele of rs10784502 in the *HMGA2* gene had **0.5% bigger intracranial volume** (9 cc, or 2 teaspoons)
- Also had **1.3 points higher full-scale IQ** per allele (N=1642; Beta(SE)=1.29(0.47); *P*=0.0073).
- This genetic variant **is associated with height**
- Has a known role in cancer cell proliferation

This result was quite widely reported (*New York Times, TIME Magazine*; 30 countries worldwide); needs to be replicated

ENIGMA-Vis

You can look up any genes or SNPs you are interested in; see if they associate with brain measures; psychiatric GWAS and mouse QTL researchers have had success with it (try it)

Nic Novak



http://enigma.loni.ucla.edu/enigma-vis/ (Novak et al., 2012)

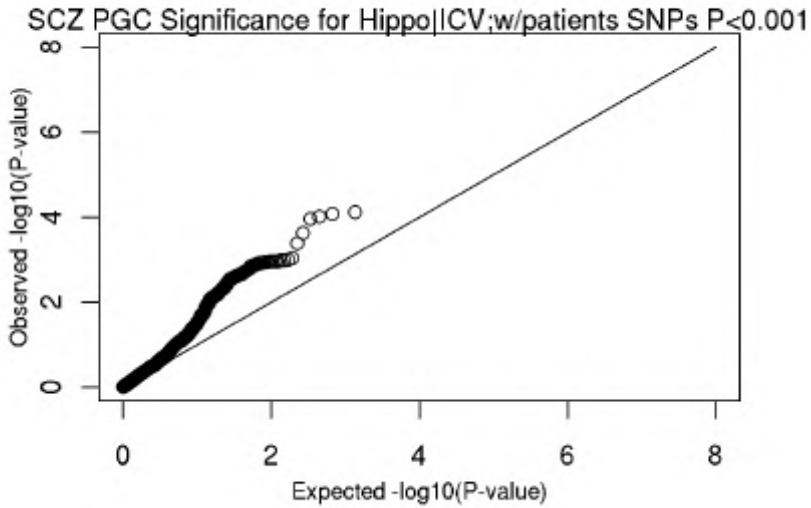
ENIGMA Working Groups

Project Name	Summary	Stage
ENIGMA2	Subcortical Morphometry (caudate, amygdala, …)	Image processing and new 1KG genetic imputation protocols now completed
ENIGMA-DTI	Diffusion Imaging Measures – integrity (FA, MD) of tracts, TBSS, anatomical connectivity, NxN connectomes	Phenotype harmonization; N=4000+; many cohorts joining; Protocol being beta-tested at 6 sites (Kochunov et al., OHBM 2012)
ENIGMA-PIB	Amyloid PET based measures	Just began – 4 large cohorts with PIB (AIBL in Australia, U. Pittsburgh, ADNI, [Wash U]) and several smaller ones
ENIGMA-PGC	How do psychiatric risk genes affect the brain? Do “brain genes” affect risk for SCZ, MDD, BPD, AUT, ADHD, …	4-pronged approach: reciprocal look-up; statistical conjunction; enrichment; polygenic testing

ENIGMA + PGC Schizophrenia
Start with simple univariate look-ups, then move on to polygenic tests, ENIGMA2 structures

Enrichment Test - QQ Plot

Do ENIGMA SNPs that may affect hippocampal volume (at $p<0.001$) affect schizophrenia risk?

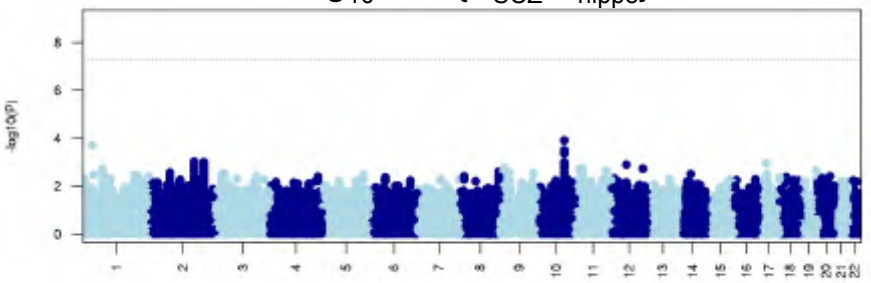


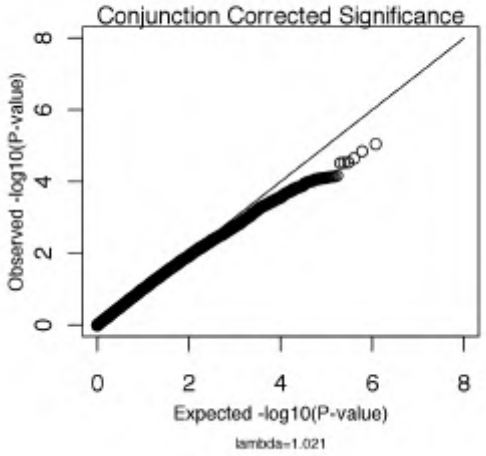
- The lambda value based on LD pruned SNPs is 1.401.
- The *P*-value for this lambda based on random draws from the LD-pruned distribution is 0.1081.
- No strong global effect of hippocampal SNPs on schizophrenia risk

Conjunction Analysis – very stringent test

Is there evidence that any SNP is associated with a change in hippocampal volume **and** risk for schizophrenia?

$-\log_{10} \max\{P_{SCZ}, P_{hippo}\}$

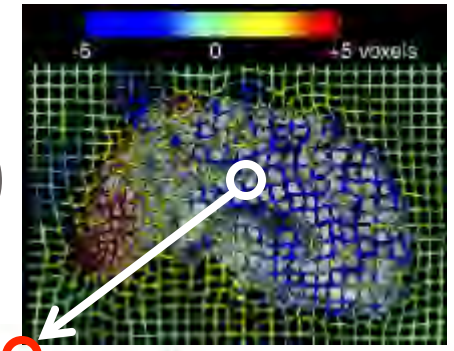


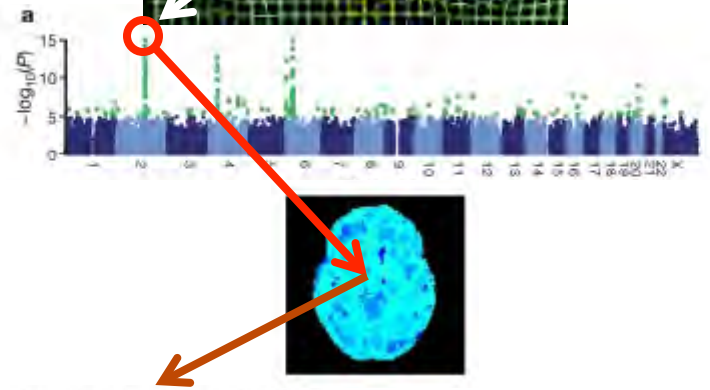


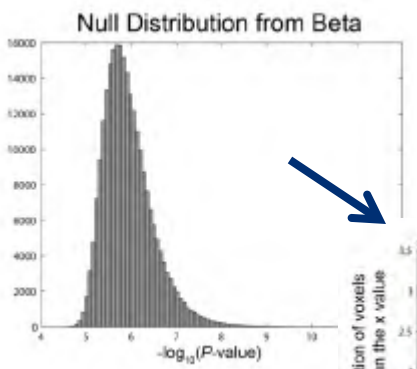
With corrected significance, no strong joint associations observed.

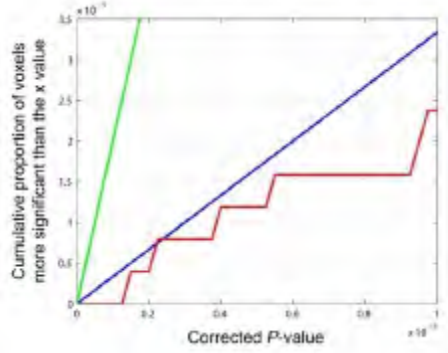
You can search the **entire brain** and the genome at the same time: "Voxelwise" GWAS (Stein 2010)

1. Volume difference at each voxel relative to a template serves as phenotype
2. Scan the genome for associations at each brain location (each voxel)
3. Select only the most associated SNP at each voxel
4. Adjust *P*-values through an inverse beta transformation (max of N null uniform distributions)
5. Correct for multiple comparisons across voxels using FDR





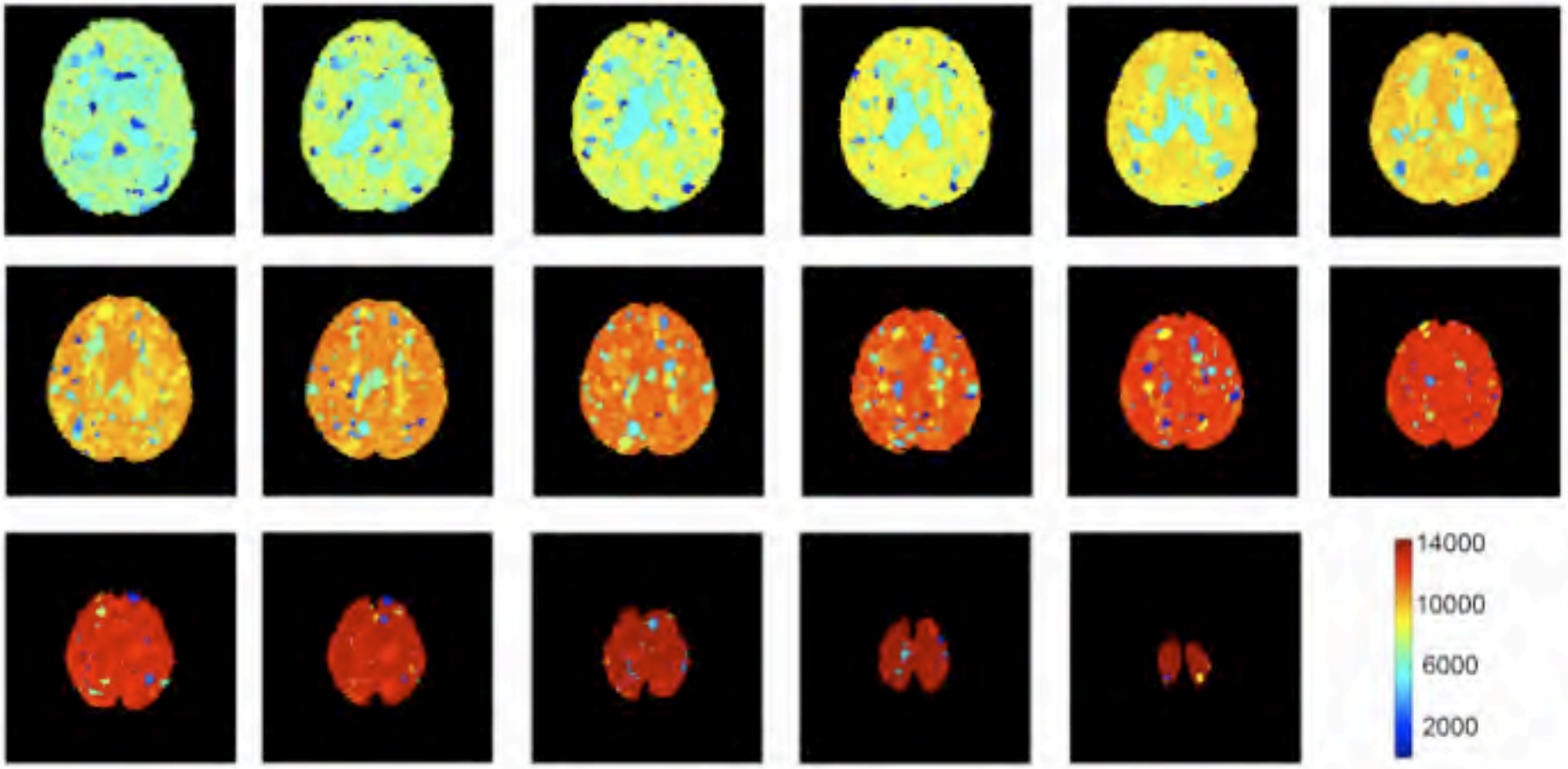




Voxelwise Genome-Wide Association Study (vGWAS; 719 subjects)

545,871 **SNPs x** 252,408 **voxels = 138 billion tests [10 days to run]**

Discovers Most Associated SNP at each Voxel



Discovered XKR4, PIP4K2A, CSMD2, CADPS2, and PIP3-E genes relevant to brain and cytoskeletal structure; some previously associated with psychiatric disease.

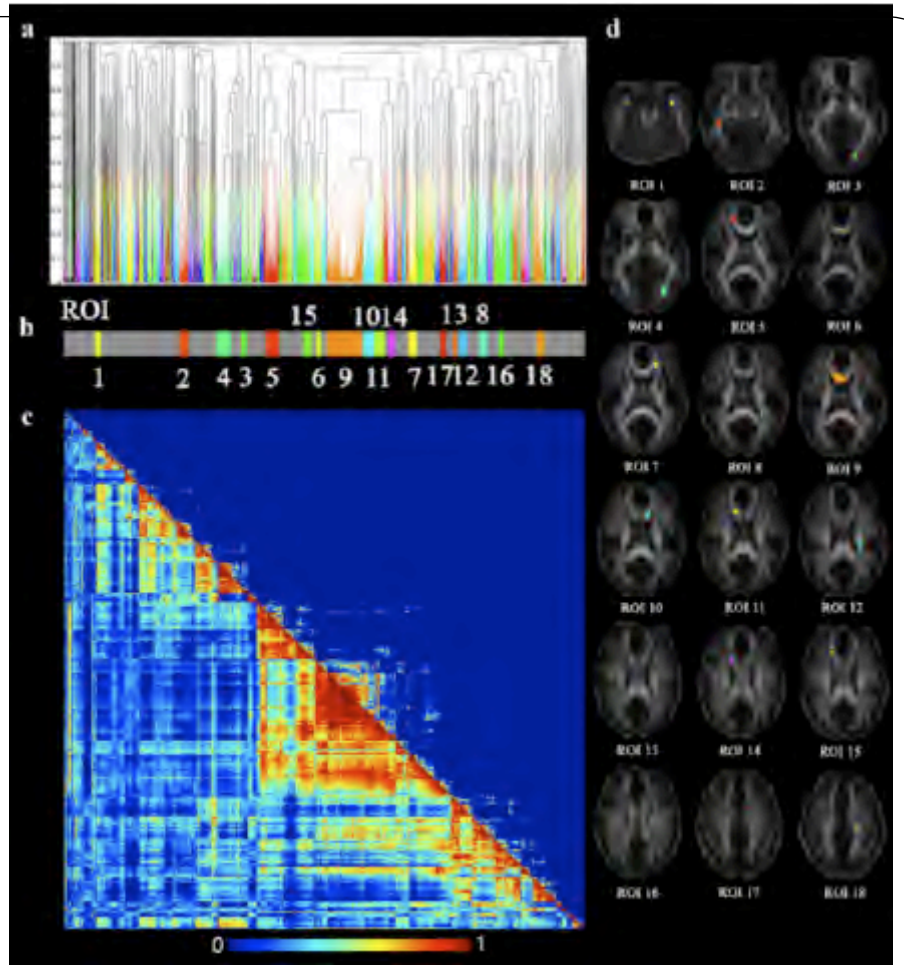
Jason L. Stein[1], Xue Hua PhD[1], Suh Lee[1], April J. Ho[1], Alex D. Leow MD PhD[1,2], Arthur W. Toga PhD[1], Andrew J. Saykin PsyD[3], Li Shen PhD[3], Tatiana Foroud PhD[4], Nathan Pankratz[4], Matthew J. Huentelman PhD[5], David W. Craig PhD[5], Jill D. Gerber[5], April N. Allen[5], Jason J. Corneveaux[5], Bryan M. DeChairo PhD[6], Steven G. Potkin MD[7], Clifford R. Jack Jr MD[8], Michael W. Weiner MD[9,10], Paul M. Thompson PhD[1,*], and the ADNI (2009). **Voxelwise Genome-Wide Association Study (vGWAS), NeuroImage 2010.**

…..but Image-wide GWAS only tests one voxel at a time, as if they were totally independent

Overlooks coherent patterns of gene action in the image

Want to Cluster Voxels with Common Genetic Influences

Boosts the Power of GWAS in Images
(Chiang et al., J Neuroscience 2012)



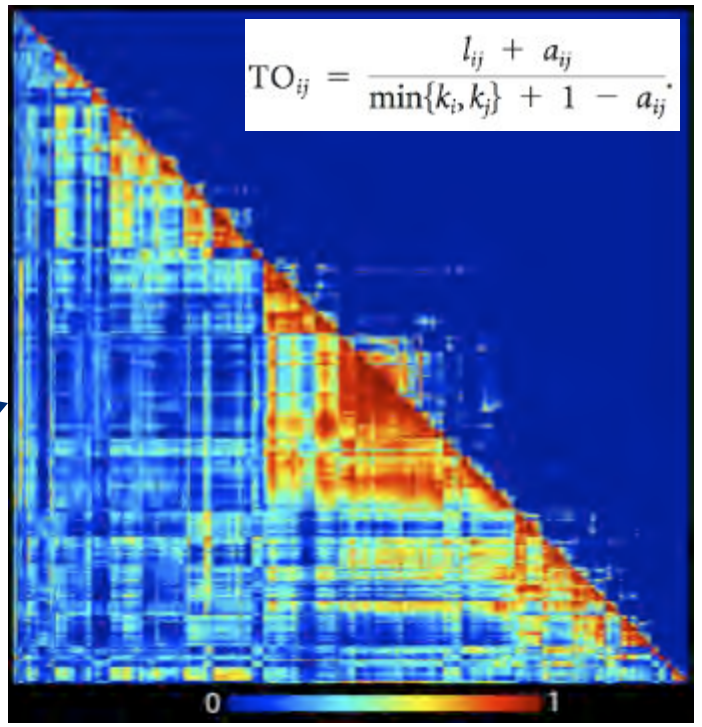
Gene Network Effects on Brain Microstructure and Intellectual Performance Identified in 472 Twins

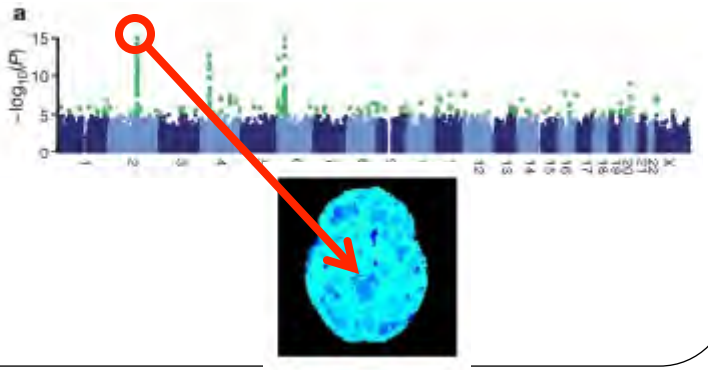
Ming-Chang Chiang,[1,2] Marina Barysheva,[2] Katie L. McMahon,[3] Greig I. de Zubicaray,[4] Kori Johnson,[3] Grant W. Montgomery,[5] Nicholas G. Martin,[5] Arthur W. Toga,[2] Margaret J. Wright,[5] Paul Shapshak,[6] and Paul M. Thompson[2]

Cluster voxels based on their genetic correlation

1. In twin or family designs, we can estimate the **genetic correlation between any two traits**, e.g. brain size and IQ, i.e., there may be a correlation between the genetic factors affecting the 2 traits
2. Apply same logic to **pairs of voxels in an image** – is there any genetic correlation? (cross-twin, cross-trait method)
3. R_g(x,y) gives very dense network; thin it down by transforming to Topological Overlap index network, TO(x,y) (Zhang & Horvath, 2005; better clusters)
4. Do hierarchical clustering of voxels with common genetic determination
5. Treat largest clusters as regions of interest
6. Run GWAS on these new ROIs
7. Much faster; does it also boost power?

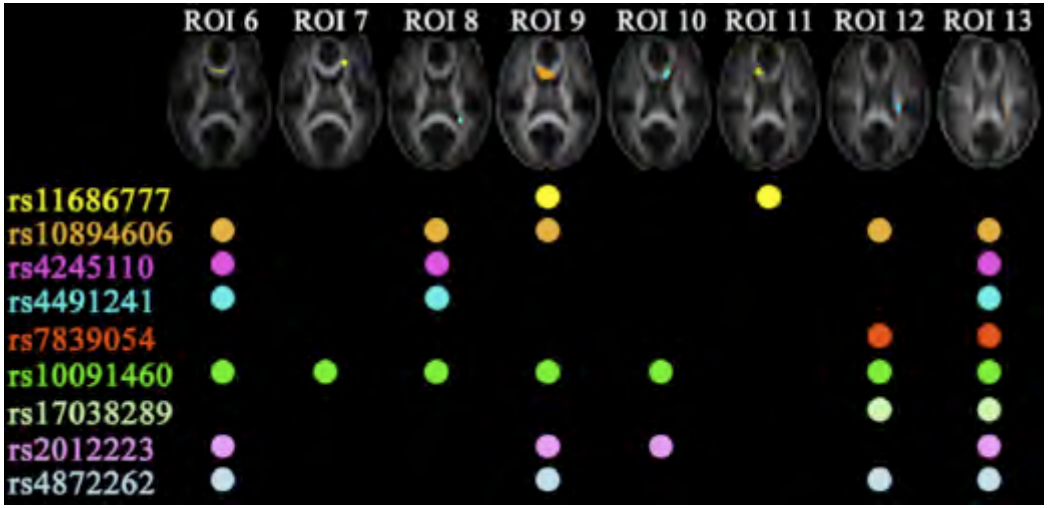
4876x4876 matrix



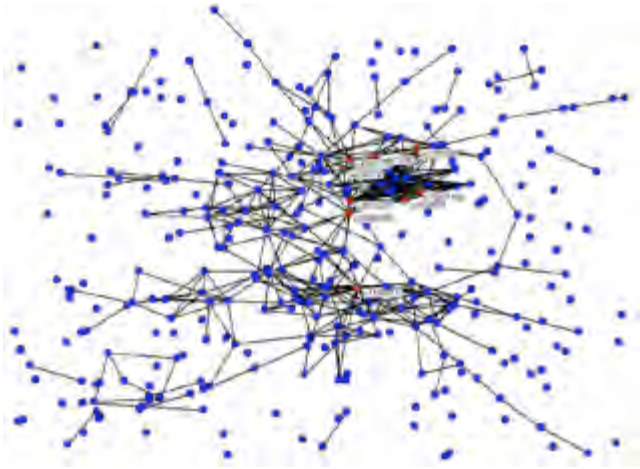


Genetic clustering boosts GWAS power

1. Many top hits now reach genome-wide significance (N=472) and replicate
2. Several SNPs affect multiple ROIs



3. Can form a network of SNPs that affect similar ROIs
4. It has a small-world, scale-free topology



(for more, see Chiang et al., J. Neurosci., 2012)

Genetic correlation between a blood biomarker and an image

1. Suppose you have a gene that affects a known blood or CSF biomarker, and you want to see if it also affects the brain, and if so, where

HFE gene -> transferrin levels in blood (buffers iron, vital for myelination)

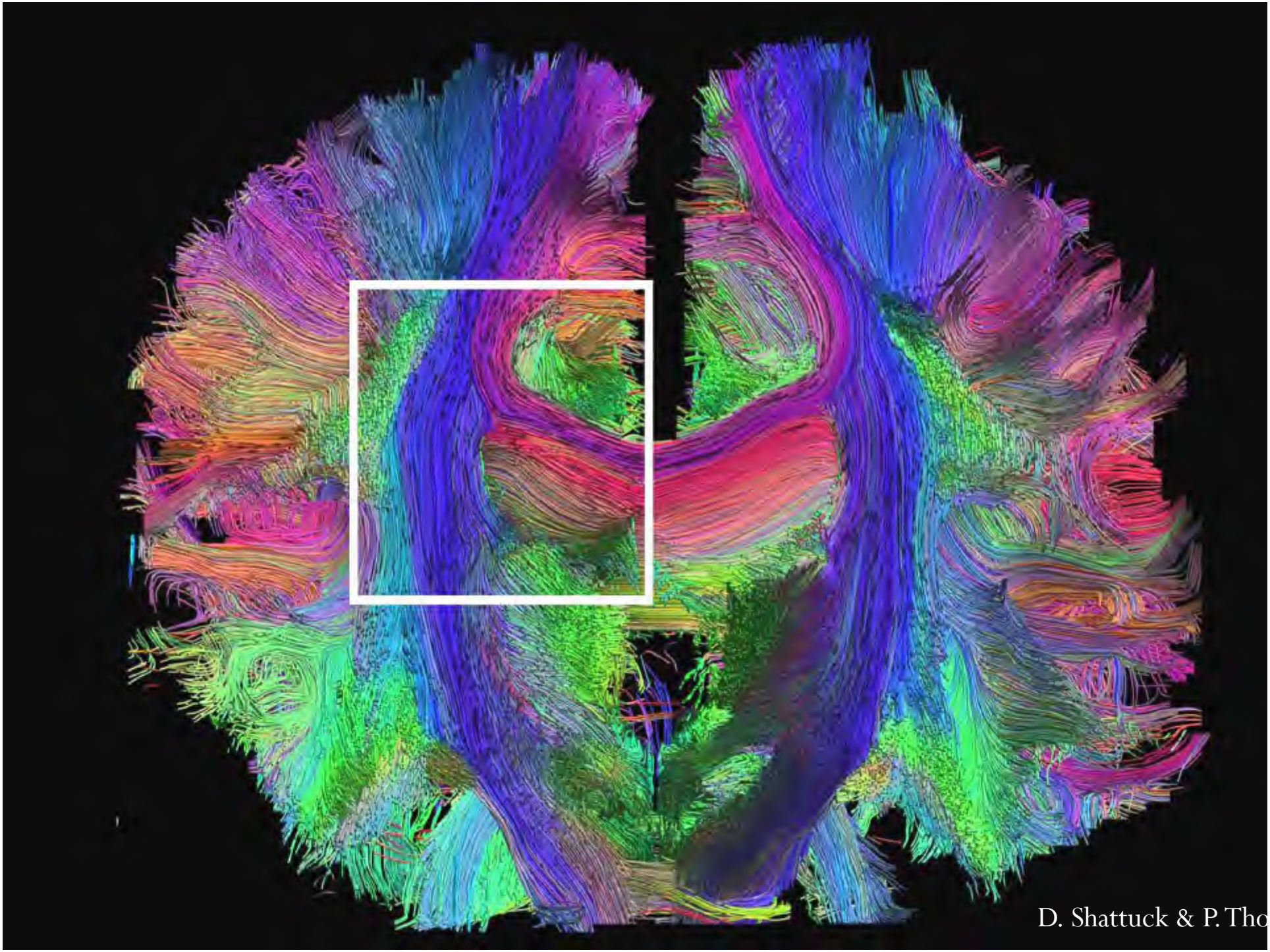
MTHFR gene -> homocysteine levels in blood (causes atrophy)

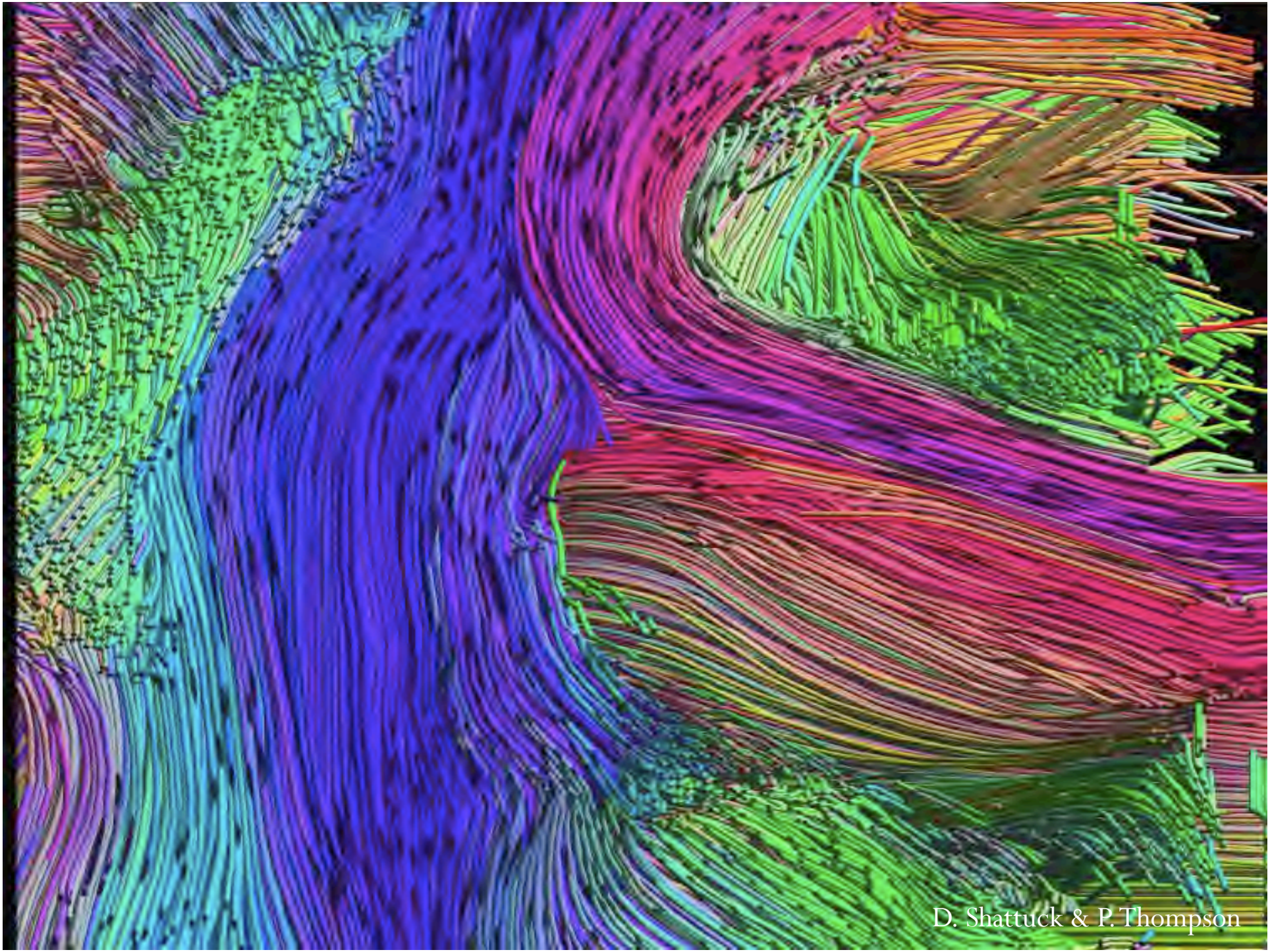
2. Find the parts of the brain that show genetic correlations with the blood measure (voxel-based cross-twin cross-trait association)
3. Test the SNP's association in just those regions of the brain, to boost power

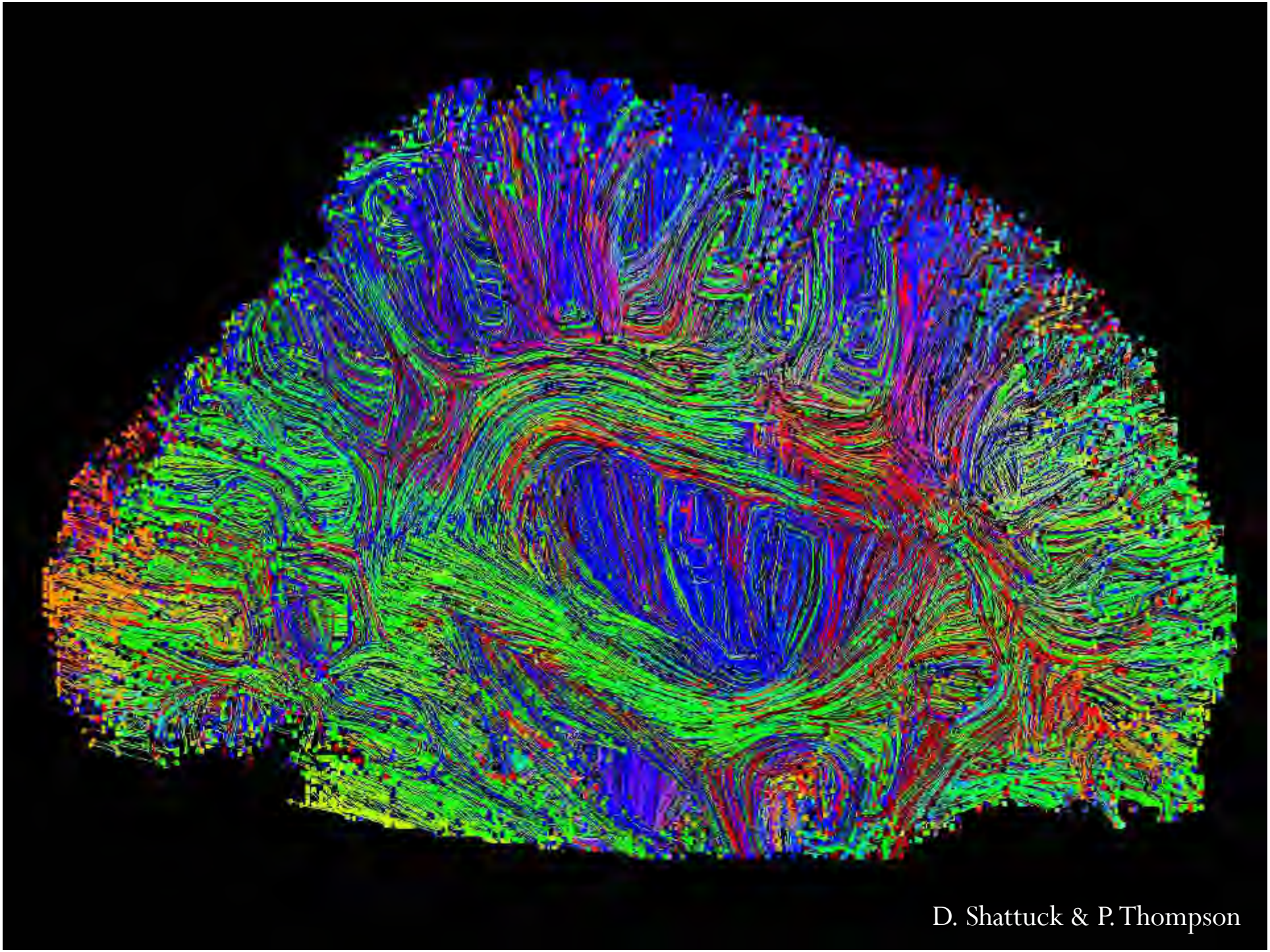
(for more, see Jahanshad et al., *PNAS*, 2011; Rajagopalan et al., submitted)

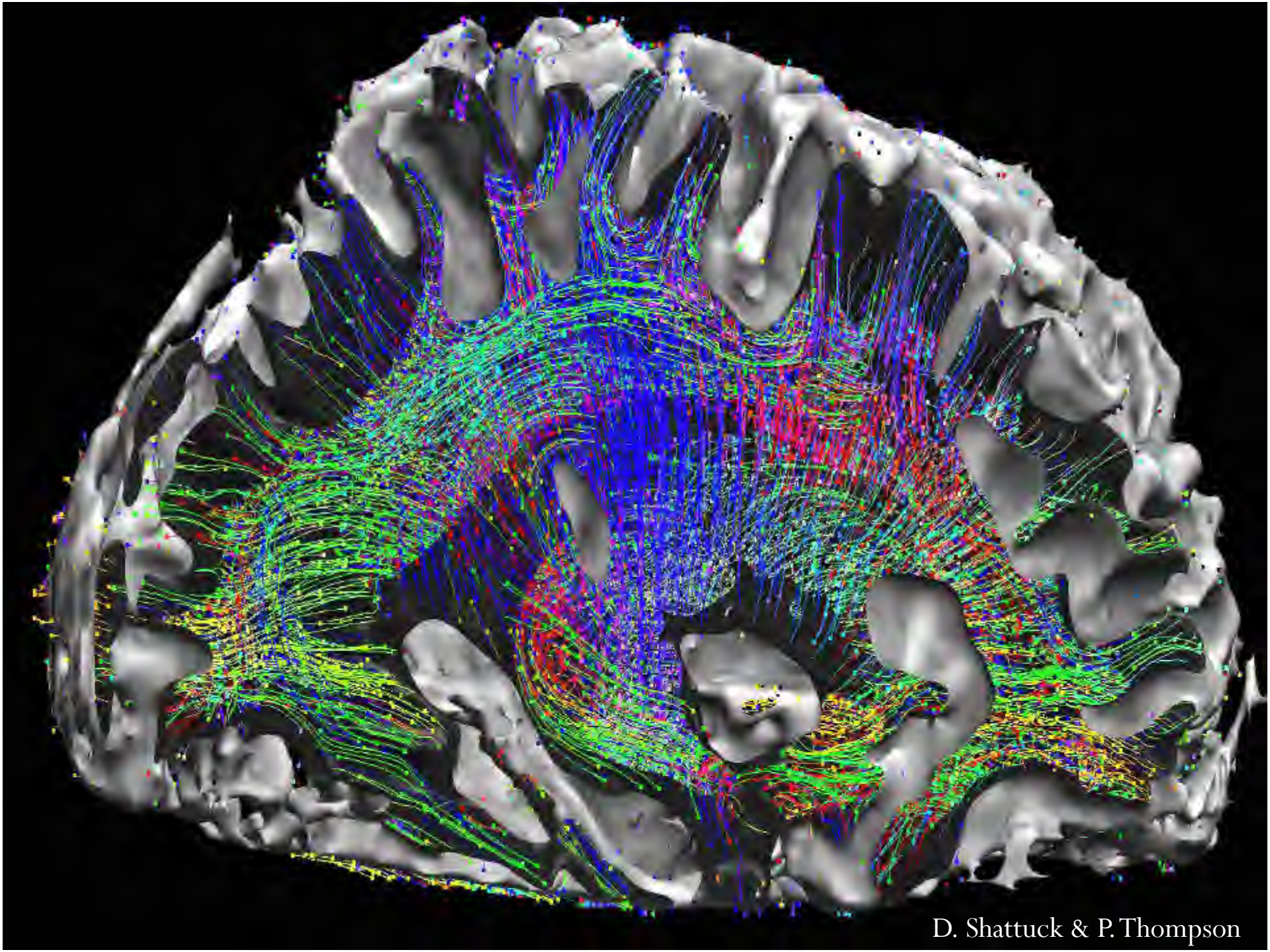
Brain structure in healthy adults is related to serum transferrin and the H63D polymorphism in the *HFE* gene

Neda Jahanshad[a,b], Omid Kohannim[a], Derrek P. Hibar[a], Jason L. Stein[a], Katie L. McMahon[c], Greig I. de Zubicaray[d], Sarah E. Medland[e], Grant W. Montgomery[e], John B. Whitfield[e], Nicholas G. Martin[e], Margaret J. Wright[e], Arthur W. Toga[a], and Paul M. Thompson[a,1]

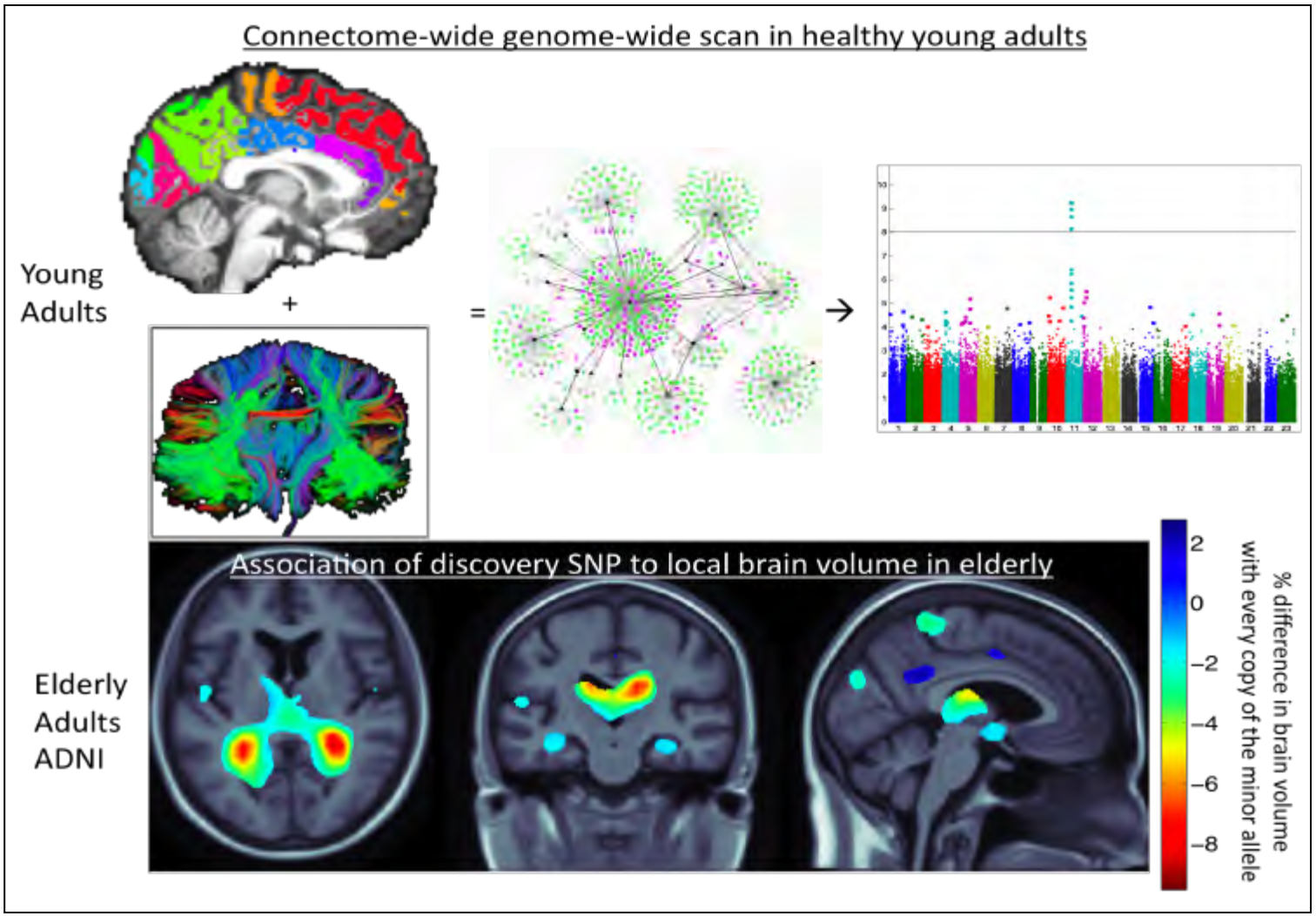

D. Shattuck & P. Tho


D. Shattuck & P. Thompson


D. Shattuck & P. Thompson


D. Shattuck & P. Thompson

Genome-Wide Screen of the Human Connectome discovers an Alzheimer risk gene (ENIGMA-DTI)



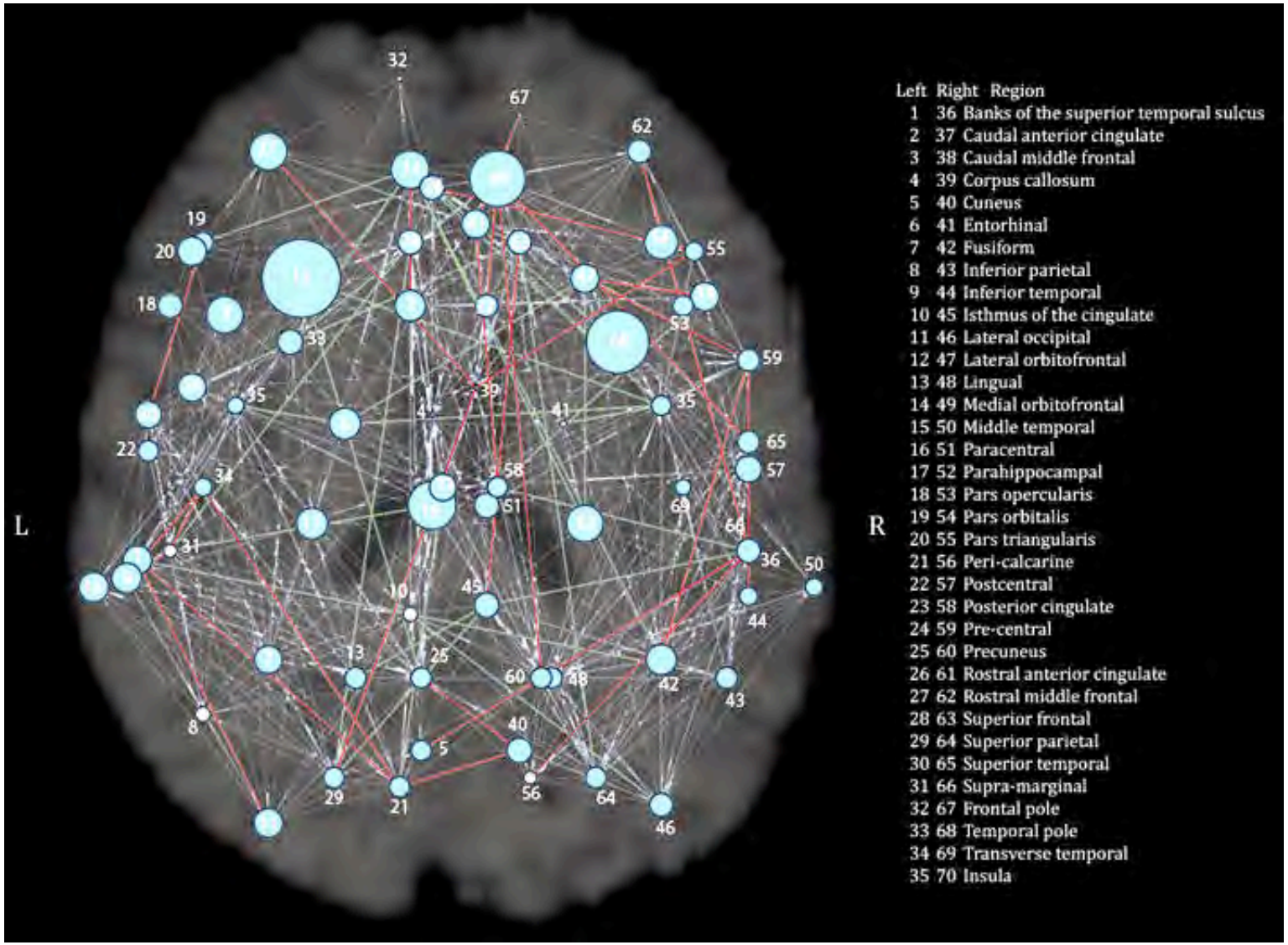
Discovery sample – Young Adults
Replication sample – ADNI

Jahanshad/Thompson, under review

Autism Risk Gene linked to Differences in Brain Wiring

CNTNAP2-CC Carriers have different networks

Circles show hubs with different eccentricity (a measure of isolation; N=328 people)



E. Dennis et al., Brain Connectivity, 2012

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